Am J Transl Res 2021;13(8):9485-9494
www.ajtr.org /ISSN:1943-8141/AJTR0128918

Original Article

Therapeutic effect of adenosylmethionine on viral hepatitis and related factors inducing diseas

Jinggui Qiao, Congya Zhao

Department of Gastroenterology, Xi'an Gaoxing Hospital, Xi'an 710000, Shaanxi Province, China

Received December 24, 2020; Accepted February 1, 2021; Epub August 15, 2021; Published August 30, 2021

Abstract: Objective: To analyze the therapeutic efficacy of adenosylmethionine on viral hepatitis and the related factors inducing disease. Methods: From May 2018 to April 2019, 137 patients with viral hepatitis who received treatment in our hospital were selected and assigned to two groups according to different treatment methods. In the control group (CG), 61 cases were treated with routine liver protection and enzyme reduction. In the research group, 76 cases were treated with adenosylmethionine on the basis of the CG. After therapy, the total response rate was analyzed in both groups, and the adverse reactions were observed during the treatment. The liver function indexes [albumin (ALB), alanine aminotransferase (ALT), glutamic acid transaminase (AST) and total bilirubin (TBIL)], liver fiber indicators [hyaluronic acid (HA), laminin (LN), type III procollagen (PCIII), type IV collagen (IV-C)], inflammatory factors [interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α)] were compared in both groups before and after therapy. ELISA was applied to detect inflammatory factors in both groups before and after treatment. Logistic analysis was applied to analyze the independent risk factors affecting the curative effect of patients with viral hepatitis. Results: After therapy, the total response rate of patients in RG was obviously higher than that in CG; The total incidence of adverse effects in RG was obviously lower than that in CG; The improvement of liver function indexes and liver fiber indicators in RG was better than that in CG; The expression of inflammatory factors in RG was obviously lower than that in CG. Logistic analysis revealed that patients' age (>40 years old), drinking history, family history, low improvement of hepatic function and hepatic fibrosis, high level of inflammatory cytokines and routine treatment were independent prognostic factors affecting patients with viral hepatitis. Conclusion: Adenosylmethionine intervention can promote disease recovery, reduce inflammation level and improve liver function damage for patients with viral hepatitis.

Keywords: Viral hepatitis, adenosylmethionine, disease recovery, inflammation level, liver function damage, factors

Introduction

Viral hepatitis is a common clinical disease [1], which is infectious in itself. The main cause of this disease is infectious diseases (mainly liver lesions) caused by various hepatitis viruses [2]. It is highly contagious and widespread, and the extremely complicated transmission route leads to the high incidence rate of the disease [3, 4]. Clinical manifestations of the disease are poor appetite, pain in liver area, discomfort in upper abdomen, nausea and fatigue, etc. [5], so it is easy to cause damage to liver function, or lead to liver cirrhosis, and even become liver cancer in severe cases [6], which has a great impact on patients' lives, and even threatens their life safety [7]. Therefore, effective intervention is particularly important.

Studies have shown that the principle of clinical intervention is mainly antiviral treatment for viral diseases [8]. At present, there are many drugs for treating this disease in clinic, but it is necessary to select drugs reasonably according to the actual situation of patients and control the dosage of drugs scientifically, so as to improve the treatment effect [9, 10]. Adenosylmethionine is a substance synthesized by adenosine triphosphate and methionine under the action of adenylyl aminotransferase [11]. It can participate in important biochemical reactions in vivo by transmethylation and transsulfation, and it has a special effect on bile transport and secretion of patients [12]. Adenosylmethionine is a kind of physiologically active molecule that exists in body tissues and body fluids, and it is involved in important biochemi-

cal reactions in human body and plays an important role [13]. Studies have revealed that it can regulate the fluidity of liver cell membrane through the methylation of plasma membrane phospholipid in liver, and promote the synthesis of sulfide in detoxification process through transsulfation, which can protect liver [14]. Studies have indicated that the adenosylmethionine intervention can effectively prevent liver injury caused by bile acid reflux and reduce the parameters of inflammatory factors for rat model of bile duct ligation [15]. Other studies have shown that adenosylmethionine has a strong membrane stabilizing effect, which can stably eliminate the manifestation of cytolysis, cholestasis and interstitial inflammatory syndrome in patients with nonalcoholic fatty liver, and it can significantly improve the albumin synthesis function of patients' liver [16].

In this research, the patients with viral hepatitis were intervened by adenosylmethionine to observe the protective effects of adenosylmethionine on the efficacy, inflammatory factors and liver function, and the risk factors affecting the efficacy, so as to provide more reference for the treatment of patients with viral hepatitis.

Materials and methods

Baseline data

From May 2018 to April 2019, 137 patients with viral hepatitis who received treatment in Xi'an Gaoxing Hospital were selected and assigned to two groups according to different treatment methods. In the control group (CG), 61 cases were treated with routine liver protection and enzyme reduction. In the research group, 76 cases were treated with adenosylmethionine on the basis of the CG.

Inclusion criteria: In both groups, patients were diagnosed with viral hepatitis [17], and the general clinical data were complete; Patients had not been systematically treated recently; In both groups, patients had stable life characteristics; Patients had the ability to think independently; Patients could correctly understand the relevant contents of the scale used in this study and give answers. This study has been approved by the ethics committee of our hospital. Both the subjects and their dependents were notified and signed the full informed consent.

Exclusion criteria were as below: Patients with severe hepatic and renal insufficiency; Comorbid with liver tumor; Severe systemic infection and other malignant tumors; Comorbid with alcoholic, cholestatic, drug-induced and autoimmune hepatitis; Pregnant and lactating women; Patients with mental illness; Those who quit the experiment halfway; Those who were not interviewed.

Treatment methods

In CG, patients were treated with conventional symptomatic treatment of protecting liver and reducing enzyme, i.e., intervention of glycyrrhizic acid preparation, reduced glutathione, vitamin K1 and potassium magnesium aspartate. Meanwhile, the disorder of water and electrolyte in the body was corrected, and the dynamic balance of body fluid was maintained. The patients were treated for 14 days.

On the basis of the CG, the ademetionine 1,4-butanedisulfonate (1000 mg) (Zhenyuan Pharmaceutical Co., Ltd., Zhejiang, China, H2014-3203) was dissolved in 5% glucose injection (100 mL), and then patients in RG were treated with intravenous infusion. The patients were treated consecutively for 14 days.

Outcome measures

1. Liver function test: The venous blood (5 mL) was drawn from the patient's elbow on an empty stomach in the morning before and after treatment for one day. The blood was centrifuged at 1500×g and 4°C for 10 min and stored in a cryogenic refrigerator at -70°C for later use. The concentrations of ALB, ALT, AST and TBIL were detected by automatic biochemical analyzer. 2. Liver fiber indexes: The serum HA, LN, PCIII and IV-C were tested by radioimmunoassay before and after treatment. 3. Inflammatory factors: The levels of IL-6 and TNF-α were tested in the two groups by ELISA [18] before and after treatment. 4. Curative effect assessment: After treatment, the patients were divided into markedly effective, effective and ineffective categories. Markedly effective: After intervention, the clinical symptoms of patients disappeared, the signs such as hepatosplenomegaly obviously subsided, and the liver function indexes, liver fiber indexes and the expression concentration of inflammatory factors decreased by more than 80% compared with those

Table 1. Comparison of patient's baseline data between the two groups [n (%)] (mean ± SD)

Classifications	RG (n=76)	CG (n=61)	t/χ^2 value	*P* value
Gender			0.161	0.688
Male	41 (53.95)	35 (57.38)		
Female	35 (46.05)	26 (42.62)		
Age/years old	45.67±4.59	45.75±4.58	0.101	0.919
BMI (kg/m^2)	22.74±2.46	22.61±2.38	0.311	0.755
Course of disease (years)	2.37±0.28	2.29±0.32	1.559	0.121
Clinical classification			0.036	0.982
Severe	23 (30.26)	18 (29.51)		
Moderate	28 (36.84)	23 (37.70)		
Acute hepatitis	25 (32.89)	19 (31.15)		
Etiologic typing			0.229	0.891
Hepatitis A	29 (38.16)	22 (36.07)		
Hepatitis B	27 (35.53)	20 (32.79)		
Hepatitis C	20 (26.32)	18 (29.51)		
Smoking history			1.441	0.229
Yes	50 (65.79)	34 (55.74)		
No	26 (34.21)	27 (44.26)		
Drinking history			0.468	0.493
Yes	52 (68.42)	45 (73.77)		
No	24 (31.58)	16 (26.23)		
Hypertension history			0.353	0.552
Yes	41 (53.95)	36 (59.02)		
No	35 (46.05)	25 (40.98)		
Diabetes history			0.231	0.630
Yes	43 (56.58)	37 (60.66)		
No	33 (43.42)	24 (39.34)		
Family history			0.017	0.893
Yes	49 (64.47)	40 (65.57)		
No	27 (35.53)	21 (34.43)		

before the treatments. Effective: After intervention, the clinical symptoms of patients disappeared, the signs such as hepatosplenomegaly improved to a certain extent, and the liver function indexes, liver fiber indexes and expression concentration of inflammatory factors decreased by <80% compared with those before treatment. Ineffective: After intervention, the patients' clinical manifestations and signs, as well as liver function indexes, liver fiber indexes and expression concentration of inflammatory cytokines were not changed or even worsened. Total response rate = (markedly effective + effective)/total cases ×100%. 5. A series of adverse effects were observed in both groups during the treatment. 6. Logistic analysis was applied to analyze the independent risk factors affecting the curative effect of patients with viral hepatitis.

Statistical methods

SPSS22.0 (Beijing Baiao Yijie Technology Co., Ltd., China) was applied for statistical analysis. GraphPad Prism 7 was applied to draw the data images. The enumeration data were represented by cases/percentage (n/%). The chi-squared test was applied for comparison of counting data between groups. When theoretical frequency in Chi-square test was less than 5, the continuous correction Chi-square test was used. The quantitative data were represented by mean ± SD. Independent-samples t test was applied for comparison of measurement data between groups. Paired t-test was applied for intra-group comparison before and after intervention. The logistics multi-factor regression analysis was applied to analyze risk factors affecting the curative effects of patients. The difference was statistically significant with P< 0.05.

Results

Baseline data

There was no obvious difference in general clinical baseline data (gender, age, body mass index, course of disease, clinical classification, etiologic typing, smoking history, drinking history, hypertension history, diabetes history and family history) between the two groups (P>0.05) (**Table 1**).

Comparison of liver function indexes between the two groups before and after therapy

There was no obvious difference in the concentrations of ALB, ALT, AST and TBIL in both groups before treatment intervention (P>0.05). After therapy, the improvement of ALB, ALT, AST and TBIL concentrations in both groups were

Table 2. Comparison of liver function indexes between the two groups before and after treatment (mean ± SD)

Grouping	Number of cases	ALB (g/L)		ALT (U/L)	
		Before treatment	After treatment	Before treatment	After treatment
RG	76	32.48±3.15	38.94±3.36	183.64±10.24	104.12±10.02
CG	61	32.69±3.17	35.28±3.33	184.02±10.31	132.68±10.07
t	-	0.386	6.362	0.215	16.540
P	-	0.699	<0.001	0.829	<0.001
Grouping	Number of cases	AST (U/L)		TBIL (μmol/L)	
		Before treatment	After treatment	Before treatment	After treatment
RG	76	103.24±10.02	35.84±3.57	42.45±4.13	24.75±2.08
CG	61	102.68±10.04	55.46±4.68	42.61±4.18	27.69±2.13
t	-	0.324	27.830	0.224	8.135
P	-	0.745	<0.001	0.823	<0.001

better than those before treatment (P<0.05), and the concentration of ALB in RG was significantly higher than that in CG (P<0.05), while the levels of ALT, AST and TBIL were obviously lower than those in CG (P<0.05) (**Table 2**).

Comparison of liver fibrosis indexes between the two groups before and after therapy

There was no obvious difference in the concentrations of HA, LN, PCIII and IV-C in both groups before treatment intervention (P>0.05). After therapy, the concentrations of HA, LN, PCIII and IV-C in both groups were obviously lower than those before treatment (P<0.05), and the concentrations of HA, LN, PCIII and IV-C in RG were obviously lower than those in CG (P<0.05) (**Figure 1**).

Comparison of inflammatory factors between the two groups before and after therapy

There was no obvious difference in the concentrations of IL-6 and TNF-α in both groups before treatment intervention (P>0.05). After therapy, the concentrations of IL-6 and TNF-α in both groups were significantly lower than those before treatment (P<0.05), and the levels of IL-6 and TNF-α in RG were obviously lower than those in CG (P<0.05) (**Figure 2**).

Comparison of therapeutic effects between the two groups after therapy

The curative effects were compared between the two groups, and the results revealed that the total response rate of RG was 94.74%, while that of CG was 77.05%. The comparison showed that the total response rate in RG was obviously higher than that in CG after therapy (P<0.05) (**Table 3**).

Comparison of adverse effects between the two groups during the treatment

The incidence of adverse effects was compared between the two groups, and the findings revealed that the total incidence of adverse effects was 3.95% in RG and 18.03% in CG. The comparison showed that the total incidence of adverse effects in RG was significantly lower than that in CG after treatment (P<0.05) (**Table 4**).

Analysis of risk factors affecting therapeutic efficacy

The differences of clinical parameters and related indexes that affect the curative effect of patients with viral hepatitis were compared. We divided the patients into two groups according to their curative effect and they were respectively included in the effective group and the ineffective group, among which 118 patients were effective after treatment and 18 patients were ineffective after treatment. Univariate analysis was conducted in patients with viral hepatitis. The results showed that there were statistical differences in age, drinking history, family history, liver function improvement, liver fiber improvement, inflammatory factor levels and treatment methods between the two groups (P<0.05). Multivariate Logistic regression analysis was conducted for the factors with differences. The results showed that age (P= 0.026), drinking history (P=0.013), family his-

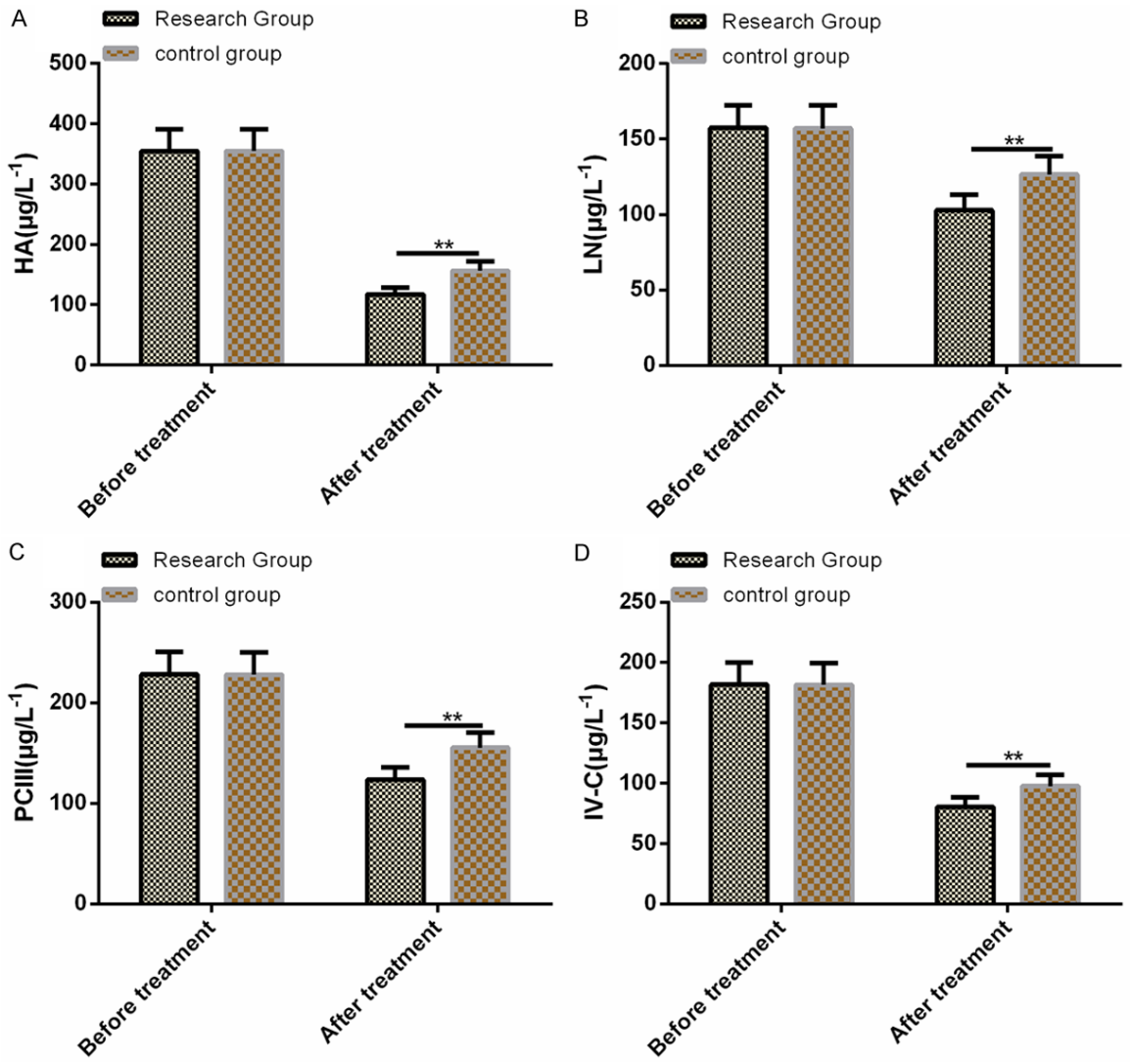

Figure 1. Comparison of liver fibrosis indexes between the two groups before and after treatment. A: There was no significant difference in the expression of HA between the two groups before treatment, but the expression of HA in RG was significantly lower than that in CG after treatment. B: There was no significant difference in the expression of LN between the two groups before treatment, but the expression of LN in RG was significantly lower than that in CG after treatment. C: There was no significant difference in the expression of PCIII between the two groups before treatment, but the expression of PCIII in RG was significantly lower than that in CG after treatment. D: There was no significant difference in the expression of IV-C between the two groups before treatment, but the expression of IV-C in RG was significantly lower than that in CG after treatment. Note: Compared with before treatment, * <0.05; Compared with the two groups after treatment, ** <0.01.

tory (P=0.015), low improvement of liver function (P=0.009), low improvement of liver fibrosis (P=0.0014), IL-6 (P=0.001), TNF-α (P= 0.001) and treatment method (P=0.001) were the risk factors influencing the efficacy of the patients. The age (>40 years old), drinking history, family history, low improvement of hepatic function and hepatic fibrosis, high level of inflammatory cytokines and routine treatment were independent prognostic factors affecting patients with viral hepatitis (P<0.05) (**Tables 5-7**).

Discussion

Viral hepatitis is a highly contagious disease [19]. Patients with viral hepatitis must be diagnosed and treated early [20]. If the treatment is not timely, the liver cirrhosis will develop, and then complications such as ascites, hepatic

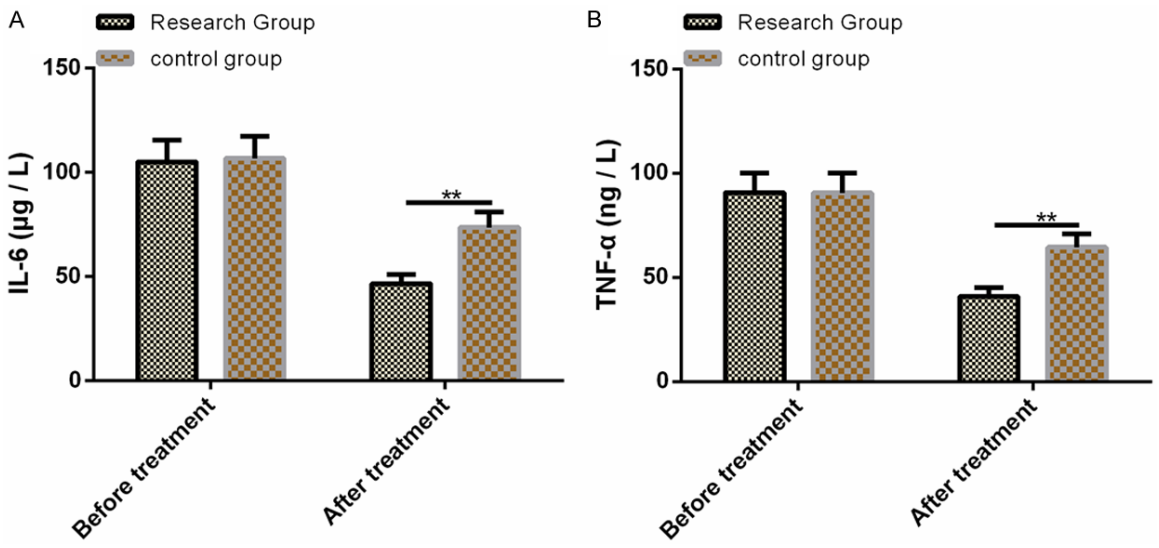

Figure 2. Comparison of inflammatory factors between the two groups before and after treatment. A: There was no significant difference in the expression of IL-6 between the two groups before treatment, but the expression of IL-6 in RG was significantly lower than that in CG after treatment. B: There was no significant difference in the expression of TNF-α between the two groups before treatment, but the expression of TNF-α in RG was significantly lower than that in CG after treatment. Note: Compared with before treatment, * <0.05; Compared between the two groups after treatment, ** <0.01.

Table 3. Comparison of therapeutic effects between the two groups after treatment [n (%)]

Grouping	Number of cases	Markedly effective	Effective	Ineffective	Total effective rate (%)
RG	76	48 (63.16)	24 (31.58)	4 (5.26)	72 (94.74)
CG	61	22 (36.07)	25 (40.98)	14 (22.95)	47 (77.05)
χ^2	-	-	-	-	9.277
P	-	-	-	-	0.002

Table 4. Comparison of adverse reactions between the two groups during treatment [n (%)]

Categories	RG (n=76)	CG (n=61)	χ^2 value	*P* value
Diarrhea	1 (1.32)	2 (3.28)	0.608	0.435
Vomiting	11 (1.32)	3 (4.92)	1.549	0.213
Nausea	11 (1.32)	4 (6.56)	2.644	0.103
Palpitation	0 (0.00)	2 (3.28)	2.529	0.111
Total incidence of adverse reactions	3 (3.95)	11 (18.03)	7.318	0.006

encephalopathy and liver cancer will develop, which will bring great threat to the life safety of patients [21]. Moreover, the pathogenesis of the disease is complex, so it will also have a serious impact on the quality of life and life safety [22]. Therefore, it is particularly important to intervene and treat viral hepatitis as soon as possible.

In this study, the patients with viral hepatitis were treated with adenosylmethionine intervention, and the results revealed that the patients' condition was improved obviously after treatment. Adenosylmethionine survives in the body fluids of patients, and belongs to physiological active factors. Its activity constituents are relatively single, mainly because adenosylmethionine participates in the biochemical reactions in patients with the combination of transmethylation and transsulfation [23]. Studies have shown that hepatitis generally have a great impact on liver function of patients, lead-

Table 5. Univariate analysis of curative effect in patients with viral hepatitis [n (%)]

Classifications	n	Effective group (n=118)	Ineffective group (n=18)	t/χ^2 value	*P* value
Age/years old				4.994	0.025
>40	73	59 (80.82)	14 (19.18)		
≤40	64	60 (93.75)	4 (6.25)		
Drinking history				5.603	0.017
Yes	97	80 (82.47)	17 (17.53)		
No	40	39 (97.50)	1 (2.50)		
Family history				5.212	0.022
Yes	89	73 (82.02)	16 (17.98)		
No	48	46 (95.83)	2 (4.17)		
Improvement of liver function				4.754	0.029
High	82	67 (81.71)	15 (18.29)		
Low	55	52 (94.55)	3 (5.45)		
Improvement of liver fibrosis index				5.890	0.015
High	78	63 (80.77)	15 (19.23)		
Low	59	56 (94.92)	3 (5.08)		
IL-6 (μg/L)	137	49.67±4.28	84.59±8.15	27.930	<0.001
TNF-α (ng/L)	137	45.16±4.07	69.23±6.19	21.640	<0.001
Treatment methods				9.277	0.002
Conventional treatment	61	47 (77.05)	14 (22.95)		
Routine+adenosylmethionine treatment	76	72 (94.74)	4 (5.26)		

Table 6. Logistic multivariate regression analysis assignment

Factors	Variables	Assignment
Age >40	X1	Yes =0, No =1
Drinking history	X2	Yes =0, No =1
Drinking history	X3	Yes =0, No =1
Improvement of liver function	X4	High =0, low =1
Improvement of liver fibrosis	X5	High =0, low =1
IL-6	X6	High =0, low =1
TNF-α	X7	High =0, low =1
Treatment methods	X8	Routine treatment =0, Routine+adenosylmethionine treatment =1

Table 7. Logistic regression analysis of multiple factors influencing curative effect of patients

Variables	B	S.E	Wals	P	OR	95% CI
Age >40	1.476	0.578	9.345	0.026	2.187	1.093-4.374
Drinking history	1.809	1.245	13.676	0.015	2.473	1.236-4.946
Drinking history	1.723	1.467	9.458	0.013	1.752	0.876-3.504
Improvement of liver function	1.913	1.024	8.446	0.009	2.247	1.123-4.494
Improvement of liver fibrosis	1.648	1.211	10.261	0.004	1.657	0.828-3.314
IL-6	1.184	0.678	8.389	0.001	1.898	0.949-3.796
TNF-α	1.843	0.245	12.137	0.001	1.795	0.897-3.590
Treatment methods	1.846	0.198	8.697	0.001	1.912	0.956-3.824

ing to an obvious increase in serum ALT, AST and other liver function indicators [24]. The finding is similar to the result of this study. This study revealed that the liver function of patients

with viral hepatitis was seriously damaged. After treatment, the ALB concentration of patients in RG was obviously higher than that in CG, and the concentrations of ALT, AST and TBIL were obviously lower than those in CG. This may be because adenosylmethionine can restore the function of normal bile excretion as soon as possible, improve the fluidity of liver cell membrane, continuously enhance the activities of Na^+, K^-, ATPase and promote the secretion and operation of bile in the organism, thus effectively alleviating liver injury. Studies have indicated that viral hepatitis can also cause liver fibrosis to varying degrees and liver cell damage. With the development of fibrosis, it will stimulate the body to synthesize lots of polyproteins, collagen, etc., which will result in the emergence of liver cirrhosis and liver cancer [25, 26]. For example, the studies by Zhang et al. have revealed that the intervention of adenosylmethionine can effectively improve the expression of hepatic function indicators and lessen liver fibrosis on rats with experimental hepatic fibrosis induced by carbon tetrachloride and ethanol [27]. This is similar to the result of this study: the liver fiber indexes of patients with viral hepatitis increased in varying degrees. After treatment, it was found that the concentrations of HA, LN, PCIII and IV-C in RG were significantly lower than those in CG, indicating that the intervention of adenosylmethionine could optimize the treatment effect and delay the progress of liver fibrosis.

Studies have shown that IL-6 is a pleiotropic cytokine, which plays a crucial role in regulating immunity and inflammatory response. The intervention of IL-6 can be used with other regulatory factors to enhance lymphocytes in vitro and contribute to the treatment of chronic hepatitis C virus infection [28]. Other studies have revealed that adenosine kinase inhibitor 5'-iodotubercidin can inhibit the inflammatory reaction of retinal pigment epithelial cells and reduce the TNF-α, IL-1β, IL-6, etc. [29]. The findings of this research revealed that the levels of IL-6 and TNF-α in RG were significantly lower than those in CG after treatment. This may be due to the fact that adenosylmethionine can suppress the activity of IL-6 and TNF-α secreted by liver cells, thus playing an anti-inflammatory role. Moreover, studies have shown that adenosylmethionine intervention has a high curative effect on the patients with complications of intrahepatic cholestasis and pregnancy, and perinatal death and adverse drug reactions develop after treatment [30]. The finding is similar to the result of this study. The results of this study showed that the total response rate of patients in RG after treatment was obviously higher than that in CG. This revealed that the clinical effect of adenosylmethionine intervention on viral hepatitis was remarkable, which could reduce the degree of liver damage, promote the recovery of hepatic function and obviously improve its clinical efficacy. After intervention, the total incidence of adverse effects in RG was significantly lower than that in CG, indicating that the adverse reactions of patients were mild by adenosylmethionine intervention. Finally, we analyzed the single factor and multiple factors that affected the efficacy of patients with viral hepatitis. The results revealed that the age (>40 years old), drinking history, family history, low improvement of hepatic function and hepatic fibrosis, high level of inflammatory cytokines and routine treatment were independent prognostic factors affecting patients with viral hepatitis.

Although this study has revealed that adenosylmethionine can bring better benefits to patients with viral hepatitis, there is still room for improvement. For example, we can include more inflammatory factors to reveal whether the intervention of adenosylmethionine can really alleviate the inflammatory response in patients with viral hepatitis, and we can further confirm the efficacy of adenosylmethionine by in vitro experiments. In the future, we will gradually carry out supplementary research from the above perspectives.

To sum up, adenosylmethionine intervention can promote disease recovery, reduce inflammation level and improve liver function damage in patients with viral hepatitis.

Disclosure of conflict of interest

None.

Address correspondence to: Congya Zhao, Department of Gastroenterology, Xi'an Gaoxing Hospital, 16 Unity South Road, Xi'an 710000, Shaanxi Province, China. Tel: +86-029-88332111; E-mail: zhaocongya2020@163.com

References

[1] Kose S, Odemis I, Celik D, Gireniz Tatar B, Akbulut I and Ciftdogan DY. Hepatitis A, B, C and HIV seroprevalence among Syrian refugee children admitted to outpatient clinics. Infez Med 2017; 25: 339-343.

[2] Ariyarathna N and Abeysena C. Sero-prevalence of viral hepatitis A in a district of Sri Lanka: a community based cross-sectional study. BMC Infect Dis 2019; 19: 443.

[3] Yoon EL, Sinn DH, Lee HW and Kim JH. Current status and strategies for the control of viral hepatitis A in Korea. Clin Mol Hepatol 2017; 23: 196-204.

[4] Bravo C, Mege L, Vigne C and Thollot Y. Clinical experience with the inactivated hepatitis A vaccine, Avaxim 80U Pediatric. Expert Rev Vaccines 2019; 18: 209-223.

[5] Abutaleb A and Kottilil S. Hepatitis a: epidemiology, natural history, unusual clinical manifestations, and prevention. Gastroenterol Clin North Am 2020; 49: 191-199.

[6] Kim MN, Hwang SG, Kim BK, Park JY, Kim DY, Han KH, Kim SU and Ahn SH. Liver cirrhosis, not antiviral therapy, predicts clinical outcome in cohorts with heterogeneous hepatitis B viral status. Gut Liver 2019; 13: 197-205.

[7] Lanini S, Pisapia R, Capobianchi MR and Ippolito G. Global epidemiology of viral hepatitis and national needs for complete control. Expert Rev Anti Infect Ther 2018; 16: 625-639.

[8] Davison J, O'Shea A, Waterbury N and Villalvazo Y. Examining hepatitis, A and B vaccination, and HBV reactivation monitoring during direct-acting antiviral therapy for hepatitis C. J Community Health 2018; 43: 1124-1127.

[9] Cao L, Liu P, Yang P, Gao Q, Li H, Sun Y, Zhu L, Lin J, Su D, Rao Z and Wang X. Structural basis for neutralization of hepatitis A virus informs a rational design of highly potent inhibitors. PLoS Biol 2019; 17: e3000229.

[10] Keck ML, Wrensch F, Pierce BG, Baumert TF and Foung SKH. Mapping determinants of virus neutralization and viral escape for rational design of a hepatitis C virus vaccine. Front Immunol 2018; 9: 1194.

[11] Strekalova E, Malin D, Weisenhorn EMM, Russell JD, Hoelper D, Jain A, Coon JJ, Lewis PW and Cryns VL. S-adenosylmethionine biosynthesis is a targetable metabolic vulnerability of cancer stem cells. Breast Cancer Res Treat 2019; 175: 39-50.

[12] Perlinska AP, Stasiulewicz A, Nawrocka EK, Kazimierczuk K, Setny P and Sulkowska JI. Restriction of S-adenosylmethionine conformational freedom by knotted protein binding sites. PLoS Comput Biol 2020; 16: e1007904.

[13] Vergani L, Baldini F, Khalil M, Voci A, Putignano P and Miraglia N. New perspectives of S-Adenosylmethionine (SAMe) applications to attenuate fatty acid-induced steatosis and oxidative stress in hepatic and endothelial cells. Molecules 2020; 25.

[14] Yamaji S, Droggiti A, Lu SC, Martinez-Chantar ML, Warner A and Varela-Rey M. S-Adenosylmethionine regulates connexins sub-types expressed by hepatocytes. Eur J Cell Biol 2011; 90: 312-322.

[15] Brzacki V, Mladenovic B, Dimic D, Jeremic L, Zivanovic D, Djukic D, Stojanovic NM and Sokolovic DT. Comparison between the effects of selenomethionine and S-adenosylmethionine in preventing cholestasis-induced rat liver damage. Amino Acids 2019; 51: 795-803.

[16] Antoniv A, Antofiychuk N, Danylyshina T, Trefanenko I and Shuper V. Clinical efficacy of S-adenosylmethionine in patients with non-alcoholic steatohepatitis and chronic kidney disease I-Ii stage. Georgian Med News 2017; 31-36.

[17] Oh HW, Cha RR, Lee SS, Lee CM, Kim WS, Jo YW, Kim JJ, Lee JM, Kim HJ, Ha CY, Kim HJ, Kim TH, Jung WT and Lee OJ. Comparing the clinical features and outcomes of acute hepatitis E viral infections with those of acute hepatitis A, B, and C infections in Korea. Intervirology 2017; 60: 109-117.

[18] Singh H, Morita T, Suzuki Y, Shimojima M, Le Van A, Sugamata M and Yang M. High sensitivity, high surface area Enzyme-linked Immunosorbent Assay (ELISA). Biomed Mater Eng 2015; 26: 115-127.

[19] Cooke GS, Andrieux-Meyer I, Applegate TL, Atun R, Burry JR, Cheinquer H, Dusheiko G, Feld JJ, Gore C, Griswold MG, Hamid S, Hellard ME, Hou J, Howell J, Jia J, Kravchenko N, Lazarus JV, Lemoine M, Lesi OA, Maistat L, McMahon BJ, Razavi H, Roberts T, Simmons B, Sonderup MW, Spearman CW, Taylor BE, Thomas DL, Waked I, Ward JW, Wiktor SZ, Lancet G and Hepatology C. Accelerating the elimination of viral hepatitis: a Lancet Gastroenterology & Hepatology Commission. Lancet Gastroenterol Hepatol 2019; 4: 135-184.

[20] Poovorawan K, Chattakul P, Chattakul S, Thongmee T, Theamboonlers A, Komolmit P and Poovorawan Y. The important role of early diagnosis and preventive management during a large-scale outbreak of hepatitis A in Thailand. Pathog Glob Health 2013; 107: 367-372.

[21] Kc S, Sharma D, Poudyal N and Basnet BK. Acute viral hepatitis in pediatric age groups. JNMA J Nepal Med Assoc 2014; 52: 687-691.

[22] Oe S, Shibata M, Miyagawa K, Honma Y, Hiura M, Abe S and Harada M. Hepatitis A complicated with acute renal failure and high hepato-

cyte growth factor: a case report. World J Gastroenterol 2015; 21: 9671-9674.
[23] Jung YS. Metabolism of sulfur-containing amino acids in the liver: a link between hepatic injury and recovery. Biol Pharm Bull 2015; 38: 971-974.
[24] Zhou L, Wang SB, Chen SG, Qu Q and Rui JA. Prognostic value of ALT, AST, and AAR in hepatocellular carcinoma with B-type hepatitis-associated cirrhosis after radical hepatectomy. Clin Lab 2018; 64: 1739-1747.
[25] Khatun M and Ray RB. Mechanisms underlying hepatitis C virus-associated hepatic fibrosis. Cells 2019; 8: 10.
[26] Besheer T, Elalfy H, Abd El-Maksoud M, Abd El-Razek A, Taman S, Zalata K, Elkashef W, Zaghloul H, Elshahawy H, Raafat D, Elemshaty W, Elsayed E, El-Gilany AH and El-Bendary M. Diffusion-weighted magnetic resonance imaging and micro-RNA in the diagnosis of hepatic fibrosis in chronic hepatitis C virus. World J Gastroenterol 2019; 25: 1366-1377.
[27] Zhang F, Gu JX, Zou XP and Zhuge YZ. Protective effects of S-adenosylmethionine against CCl_4 - and ethanol-induced experimental hepatic fibrosis. Mol Biol (Mosk) 2016; 50: 284-290.
[28] Naseem S, Manzoor S, Javed A and Abbas S. Interleukin-6 rescues lymphocyte from apoptosis and exhaustion induced by chronic hepatitis C virus infection. Viral Immunol 2018; 31: 624-631.
[29] Qin S, Ni M and De Vries GW. Implication of S-adenosylhomocysteine hydrolase in inhibition of TNF-alpha- and IL-1beta-induced expression of inflammatory mediators by AICAR in RPE cells. Invest Ophthalmol Vis Sci 2008; 49: 1274-1281.
[30] Zhang L, Liu XH, Qi HB, Li Z, Fu XD, Chen L and Shao Y. Ursodeoxycholic acid and S-adenosylmethionine in the treatment of intrahepatic cholestasis of pregnancy: a multi-centered randomized controlled trial. Eur Rev Med Pharmacol Sci 2015; 19: 3770-3776.