DOI http://doi.org/10.30978/UTJ2025-2-18
УДК 616.12-008.331.1+616.36-003.836-008.9]-036.1-085

ISSN 1605-7295 (Print)
ISSN 2522-1175 (Online)

Clinical efficacy of S-adenosyl-L-methionine and antihypertensive combination treatment in patients with comorbid course of metabolic-associated steatotic liver disease and arterial hypertension

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Objective — to determine the likely effect of S-adenosyl-L-methionine (SAMe) and antihypertensive combination treatment on the clinical course, liver enzymatic activity (the levels of aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, alkaline phosphatase), nonalcoholic steatohepatitis activity and the stage of liver fibrosis (LF) stage in patients with metabolic dysfunction-associated steatotic liver disease (MASLD) and arterial hypertension (AH) comorbid course.

Materials and methods. We examined 40 patients with MASLD and AH comorbid course before and after 5 months of the SAMe and antihypertensive combination treatment. The control group comprised 20 apparently healthy people. Patients with viral hepatitis, liver cirrhosis, alcoholic liver disease, AH stage III, and liver fibrosis stage F3—4 were excluded. Liver cytolysis indicators analyses were performed using biochemical techniques. The severity of liver fibrosis was assessed using transient elastography results.

Results. Analysis of SAMe and antihypertensive combination treatment in patients with MASLD and AH demonstrated a significant improvement in the clinical course of the disease (reduction in complaints of increased fatigue, headache, general weakness, right upper quadrant pain, sleep disturbance and mood worsening ($p < 0.05$)), significant decrease of systolic blood pressure ($p < 0.01$), diastolic blood pressure ($p < 0.05$), body mass index ($p < 0.05$) and waist-to-hip ratio ($p = 0.05$), liver cytolysis indicators such as aspartate aminotransferase ($p < 0.01$), alanine aminotransferase ($p < 0.01$), gamma-glutamyl transpeptidase ($p < 0.01$) and alkaline phosphatase ($p < 0.05$). Also, a decrease in nonalcoholic steatohepatitis activity ($p < 0.05$) and regression of the liver fibrosis stage ($p < 0.05$) were observed.

Conclusions. The results of SAMe and combined antihypertensive therapy show the improvement of the clinical course of the disease, liver function, and the regression of the liver fibrosis stage. Therefore, the inclusion of SAMe in standard antihypertensive therapy of patients with a comorbid course of MASLD and AH is an appropriate treatment method as a pathogenetic drug with a pronounced cytoprotective, anti-inflammatory, and antifibrotic effect.

Keywords:
metabolic dysfunction-associated steatotic liver disease, arterial hypertension, liver fibrosis, non-alcoholic steatohepatitis, S-adenosyl-L-methionine.

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Отримано • *Received*
09/04/2025
Прийнято до друку • *Accepted*
30/04/2025
Опубліковано • *Published*
19/06/2025

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The prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD), defined by a broad spectrum of liver damage ranging from simple steatosis to progressive nonalcoholic steatohepatitis (NASH), liver fibrosis (LF), and cirrhosis, is increasing every year in patients with obesity and other metabolic syndromes [9]. NASH is characterized by hepatocellular damage involving steatosis, inflammation, and LF. It is a significant risk factor for

cirrhosis and hepatocellular carcinoma (HCC), and it significantly increases the risk of death due to liver-related causes [2]. Currently, there are no approved guidelines for the treatment of NASH and current therapies are limited to lifestyle interventions (calorie restriction, exercise) and treating comorbidities, such as insulin resistance, obesity, etc. Due to low patient compliance and the growing obesity epidemic, the number of patients diagnosed with MASLD and NASH continues to grow [19].

According to basic medical studies, many factors are involved in the MASLD progression. For instance, accumulating evidence has proposed that the renin-angiotensin system (RAS) is involved in hepatic fibrogenesis and inflammation [2]. Angiotensin II (Ang II), the leading biologically active product of the RAS, and angiotensin II type 1 receptor (AT1R) were determined to promote MASLD, and previous studies have illustrated that AT1R blockade can ameliorate fatty liver and that AT1R blockers can potentially be used for MASLD therapy [4]. Another factor in the progression of MASLD is the impaired metabolism of S-adenosyl-L-methionine (SAMe), in the production of which the liver performs a fundamental task. Although all mammalian cells and tissues convert methionine to homocysteine via SAMe, the liver is where the bulk of SAMe is generated as it is the organ where about 50 % of all dietary methionine is metabolized and where up to 85 % of all transmethylation reactions take place [7]. As a methyl supplement, SAMe participates in multiple biological processes and alters chemical modifications of the genome and proteins [10]. SAMe has been demonstrated to provide clinical benefits in chronic liver disease and induces the methylation of phospholipids, which performs a crucial task in the metabolisms of lipids [8].

Also, another one molecular mechanism in the pathogenesis of NASH is the reduction in the level of Glycine-N-methyltransferase (GNMT), which is the most abundant methyltransferase in the liver [15]. It catalyzes the transfer of a methyl group from SAMe, the universal methyl donor, to glycine to form sarcosine. The importance of GNMT in the progression of MASLD has been demonstrated in several studies. In a study by C. C. Hughey et al. (2018), GNMT has been identified to be downregulated both in MASLD and HCC [11]. In a study by M. Luz Martínez-Chantar (2008), it was determined that GNMT-deficient mice developed steatosis, fibrosis, and HCC [13].

SAMe deficiency is found in all chronic liver diseases, including MASLD, in which it can participate as a precursor for glutathione and a donor of methyl groups in the synthesis of phosphatidylcholine, which is necessary for the export of triglycerides (TG) from the hepatocyte [1]. Thus, a study by M. Martinez-Una et al. (2016) demonstrated that low hepatic levels of SAMe in mice reduced TG secretion, which contributes to hepatosteatosis [14]. Data from several clinical studies on the use of SAMe in chronic liver diseases suggest its effectiveness in NASH, including in the stage of liver fibrogenesis. Thus, the results of a randomized clinical trial by Tao Guo et al. (China, 2015) report that the administration of SAMe improves liver function and can be the basis of therapy for its pathology [8].

Recently, the study of the mechanisms of MASLD progression in patients with concomitant arterial hypertension (AH) has attracted considerable attention from scientists. AH is a multifactorial disease that results from the interaction between genetic predisposition and environmental risk factors [17]. Current epidemiological data have demonstrated that about 49.5 % of patients with AH have MASLD, and the prevalence of AH is significantly higher in patients with MASLD than in the general population [5]. The main reason for the increased mortality of patients with MASLD and AH is the development of cardiovascular diseases (CVD) [18]. It is reported that one of the mechanisms that significantly increases the risk of developing CVD, cardiovascular catastrophes, and premature death of patients is the comorbid course of MASLD and AH [12].

Currently, the mechanisms of drug correction of this comorbid pathology remain poorly understood. Therefore, the search for effective treatment regimens for patients with combined MASLD and AH is a relevant issue of modern internal medicine.

Objective — to determine the likely effect of SAMe and antihypertensive combination treatment on the clinical course, liver enzymatic activity (the levels of aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, alkaline phosphatase), nonalcoholic steatohepatitis activity and influence on the liver fibrosis stage in patients with metabolic dysfunction-associated steatotic liver disease and arterial hypertension stage I—II comorbid course.

Materials and methods

The examined contingent of patients consisted of 40 patients, who were divided into the following groups: the main group — 40 patients with comorbid MASLD and AH before SAMe and antihypertensive combination treatment, the comparison group — 40 patients with comorbid MASLD and AH after treatment, the control group — 20 relatively healthy individuals.

The study was performed in compliance with the main provisions of the «Rules of Ethical Principles for Conducting Scientific Medical Research with Human Participation», approved by the Declaration

of Helsinki (1964—2013), ICH AHP (1996), EEC Directive No. 609 (dated 11/24/1986), orders of the Ministry of Health of Ukraine No. 690 dated 09/23/2009, No. 944 dated 12/14/2009, No. 616 dated 08/03/2012. All participants were informed about the goals, organization, and methods of the study and signed an informed consent to participate in it, all measures were taken to ensure the anonymity of patients.

All patients were given recommendations for correction of the diet, calorie intake, systematic physical activity, and rest. To assess the impact of the proposed treatment, patients with comorbid MASLD and AH stage I were prescribed ademetionine at a dose of 800 mg intravenously for the first 10 days, followed by tablet form — 400 mg 2 times a day and perindopril at a dose of 10 mg/day. Patients with comorbid MASLD and AH stage II were prescribed ademetionine at a dose of 800 mg intravenously for the first 10 days, followed by tablet form — 400 mg 2 times a day and a combination of antihypertensive drugs: perindopril (as perindopril tosylate) at a dose of 10 mg/day and indapamide at a dose of 2.5 mg/day. The duration of treatment with ademetionine was 5 months.

All patients underwent a medical and life history, complaints, and a survey on alcohol consumption using the UK Chief Medical Officers' Low-Risk Drinking Guidelines questionnaire. All patients underwent anthropometric measurements (weight, height, body mass index (BMI), waist circumference (WC), hip circumference (HC), Waist-to-Hip Ratio (WHR)), measurement of systolic blood pressure (SBP), diastolic blood pressure (DBP), biochemical liver function tests (aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP)) and assessment of the severity of LF.

Exclusion criteria from the study were: serologically confirmed infectious liver diseases (including viral hepatitis B and C), primary biliary cirrhosis, sclerosing cholangitis, use of hepatotoxic drugs, alcohol consumption of more than 3—4 alcoholic units per day for men and 1—2 alcoholic units per day for women, presence of signs of liver failure, such as ascites, hepatic encephalopathy, bleeding from esophageal varices, and others. The study also excluded patients with chronic inflammatory diseases, diabetes, obesity, chronic heart failure, autoimmune rheumatological diseases, thyroid diseases, cancer, renal failure, pregnant women, and patients over 55 years of age.

The diagnosis of AH was established following the order of the Ministry of Health of Ukraine dated 12.09.2024 No. 1581 «On approval of the Unified Clinical Protocol of Primary and Specialized Medical Care «Hypertensive Disease (Arterial Hypertension)» and the criteria of the European Clinical Guidelines (ESH/ESC) on Arterial Hypertension, 2024. The degree and stage of AH were determined based on the guidelines of the European Society of Cardiology on the clinical practice of managing patients with Arterial Hypertension (ESC/ESH Clinical Practice Guidelines, 2024).

The diagnosis of MASLD in the steatosis stage was established based on the ultrasound method of liver examination, the criteria of the European Association for the Study of Liver Diseases (EASL, 2024), the American Association for the Study of Liver Diseases (AASLD, 2023). Also, to verify liver steatosis, biomarkers such as the calculation of the fatty liver index, the MASLD liver fat score, and the hepatic steatosis index were used.

The diagnosis of MASLD in the NASH stage was determined based on the Order of the Ministry of Health of Ukraine dated November 6, 2014 No. 826 «Unified clinical protocol for primary, secondary (specialized) medical care: non-alcoholic steatohepatitis», the European Association for the Study of Liver Diseases (EASL, 2024), the American Association for the Study of Liver Diseases (AASLD, 2023), determination of liver enzyme activity (AST, ALT, AST/ALT ratio, GGT, ALP), as well as determination of interleukin-6, interleukin-4, C-reactive protein levels. Also, for the verification of NASH, the GULAB scale was used, which is based on the results of liver ultrasound, lipid spectrum indicators, ALT level, and BMI determination, as well as considering the patient's gender.

The assessment of the severity of LF was carried out according to the results of transient elastography (TE) and corresponded to the values of the international METAVIR scale, where F0 is the absence of fibrosis, F1 is portal fibrosis (stellate expansion of the portal tracts) without septa, F2 is portal fibrosis and single septa, F3 is portal fibrosis and multiple septa without cirrhosis, F4 is cirrhosis. TE of the liver was performed using an expert-class ultrasound scanner — Siemens-Acusons 3000 («Radmir», Kharkiv, Ukraine) with a convex format sensor at frequencies of 2—5 MHz at a depth of 10—50 mm from the capsule.

The average age of the studied patients was 49.36 ± 8.5 years, the number of men was 45 % (n = 18), and women — 55 % (n = 22). The average duration of AH in patients of the main group was 8.5 ± 1.2 years, MASLD — 7.2 ± 3.5 years.

The results statistical processing was performed with Microsoft Office Excel 2013 and Statistica 13.1 computer programs on a personal computer with the use of parametric (Student's t-test) and non-parametric (Mann–Whitney U-test) statistical methods. Evaluation of correlations was carried out according to Spearman's rank correlation coefficient R [6]. In the studied groups' comparison, the error probability was considered to be statistically significant at $p \leq 0.05$.

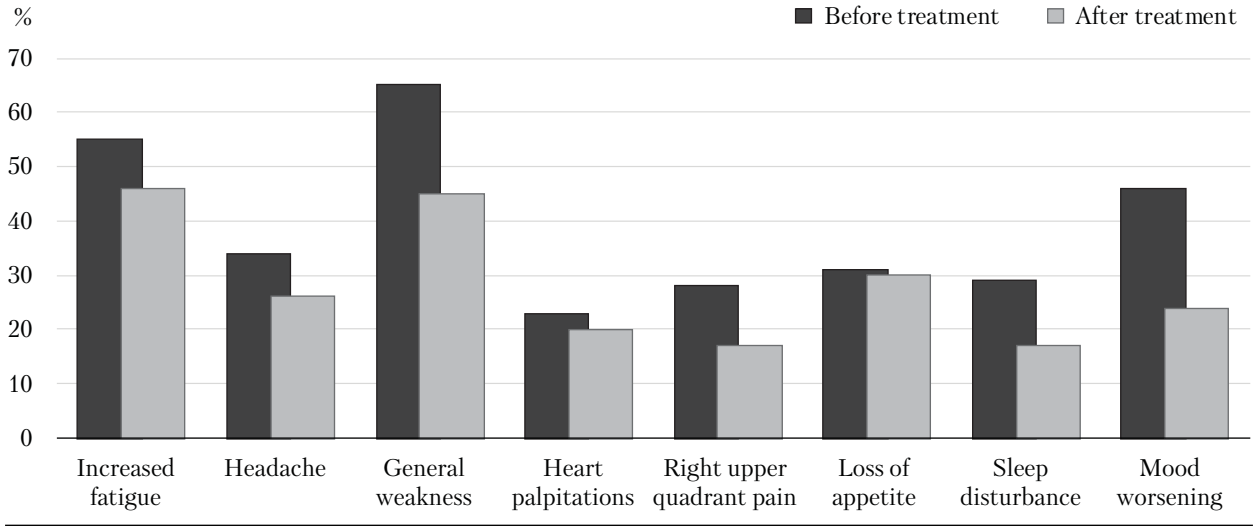

Figure 1. Results of SAMe and antihypertensive combination treatment on the clinical course of the disease in patients with MASLD and AH

Results

The effect of SAMe and antihypertensive combination treatment on the clinical course of the disease

Analysis of the results of SAMe and antihypertensive combination treatment in patients with MASLD, which proceeds on the background of AH, demonstrated a significant reduction in such complaints as: increased fatigue, headache, general weakness, aching pain in the right hypochondrium, decreased appetite, sleep disorders and mood deterioration. Thus, the main complaints of patients in the group before treatment were (Fig. 1): increased fatigue in 55 % of patients, headache (34 % of patients), heart palpitations (23 % of patients), general weakness (65 % of patients), right upper quadrant pain (28 % of patients), loss of appetite (31 % of patients), sleep disturbance (29 % of patients), mood worsening (34 % of patients).

After treatment, the group of studied patients reported a reduction in complaints of increased fatigue by 9 % ($p < 0.05$), headache by 8 % ($p < 0.05$), general weakness by 20 % ($p < 0.05$), right upper quadrant pain by 11 % ($p < 0.05$), sleep disturbance by 12 % ($p < 0.05$) and mood worsening by 22 % ($p < 0.05$). However, when comparing the results of the treatment effect on the dynamics of complaints of heart palpitations ($p > 0.05$) and loss of appetite ($p > 0.05$), no significant changes were recorded.

The effect of SAMe and antihypertensive combination treatment on the blood pressure average values, BMI and WHR

In patients with comorbid MASLD and AH, a significant decrease in SBP, DBP, BMI, and WHR levels was found after treatment compared to baseline data for this group of patients (Table).

Thus, in patients with MASLD and AH, a decrease of SBP was observed against the background of combined treatment from 145.5 ± 10.0 mm Hg to 125.5 ± 5.0 mm Hg ($p < 0.01$). The mean DBP in the studied patients was on average reduced from 105.3 ± 10.0 mm Hg to 90.6 ± 5.0 mm Hg ($p < 0.05$). In addition, in patients with comorbid pathology, after providing recommendations for correction of the diet, calorie intake, systematic physical activity, and rest, as well as the appointment of combined therapy, a significant decrease in mean BMI and WHR was detected. Thus, after the SAMe and antihypertensive combination treatment, the average

Table. The studied patient groups' anthropometric characteristics before and after the SAMe and antihypertensive combination treatment (μ ± SD)

Parameter	Control group (n = 20)	MASLD and AH (n = 40)		
		Before treatment	After treatment	p
SBP, mm Hg	120.0 ± 5.0	145.5 ± 10.0	125.5 ± 5.0	< 0.01
DBP, mm Hg	80.5 ± 5.0	105.3 ± 10.0	90.6 ± 5.0	< 0.05
BMI, kg/m^2	23.9 ± 2.35	28.3 ± 2.14	26.9 ± 3.27	< 0.05
WHR	0.87 ± 0.5	2.5 ± 0.8	1.09 ± 0.7	0.05

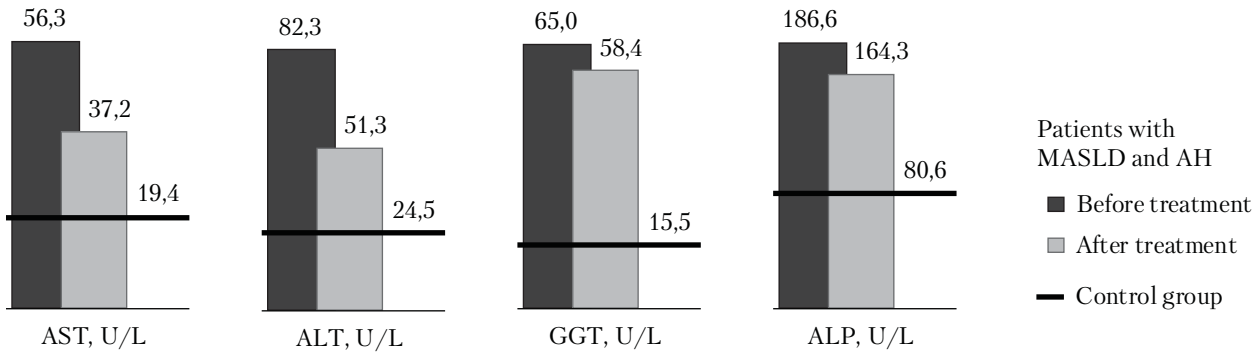

Figure 2. Results of SAMe and antihypertensive combination treatment on the liver cytolysis indicators in patients with MASLD and AH

BMI values among patients with MASLD and AH were reduced from 28.3 ± 2.14 kg/m² to 26.9 ± 3.27 kg/m² ($p < 0.05$). The average values of the WHR in patients with comorbid pathology were reduced from 2.5 ± 0.8 to 1.09 ± 0.7 ($p = 0.05$).

The effect of SAMe and antihypertensive combination treatment on the liver cytolysis indicators, NASH, and liver fibrosis stages

After 5 months from the start of combined SAMe and antihypertensive therapy, a significant decrease in liver cytolysis indices was observed in patients with MASLD and AH (Fig. 2).

Thus, the mean values of AST levels in the group of patients with comorbid pathology were reduced from 56.3 ± 10.2 to 37.2 ± 12.5 IU/L ($p < 0.01$). The mean values of ALT levels in the studied patients were also reduced from 82.3 ± 12.4 to 51.3 ± 11.8 IU/L ($p < 0.01$). The mean values of GGT against the background of the proposed treatment decreased from 65.0 ± 16.4 to 58.4 ± 12.5 IU/L ($p < 0.05$), and the mean values of ALP decreased from 186.6 ± 27.9 to 164.3 ± 17.5 IU/L ($p < 0.05$).

It was also proven that 5 months after the start of SAMe use, positive dynamics were observed in the regression of NASH and LF in the group of patients with MASLD and AH (Fig. 3).

Thus, the number of patients in the stage of LF F1—2 decreased from 23.8% to 15.0% ($p < 0.05$), the number of patients in the stage of fibrosis F0—1 decreased from 26.1% to 17.0% ($p < 0.05$), the number of patients in the stage of NASH decreased from 23.8% to 14.0% ($p < 0.05$). Thus, the obtained results of the SAMe treatment demonstrate the participation of this drug in the regression of the stages of MASLD.

Discussion

This study showed the presence of a positive impact of SAMe and antihypertensive combination treatment on the clinical course of the disease, a significant decrease of systolic and diastolic blood pressure, reduction of BMI and WHR. A significant decrease in liver cytolysis indicators such as AST ($p < 0.01$), ALT ($p < 0.01$), GGT ($p < 0.01$) and ALP ($p < 0.05$) was observed. Also, the results of SAMe and antihypertensive combination treatment demonstrated a decrease of NASH activity and regression of the LF stages in the studied patients. Previous studies demonstrate that using SAMe has a pronounced therapeutic effect to correct hepatic dysfunction [16]. In the study by Tao Guo et al. (2015) it was demonstrated that SAMe decreased the AST levels in patients with chronic liver diseases [8]. In the study by A. Antoniv et al. (2017), it was demonstrated that SAMe produces powerful membrane-stabilizing effects on the affected hepatocytes, reduces the intensity of cytolysis, cholestasis, mesenchymal-inflammatory syndrome, and inhibits the progression of hepatic dysfunction in patients with NASH [1]. Also, in the study by İ. Bingül et al. (2024), it was demonstrated that SAMe treatment

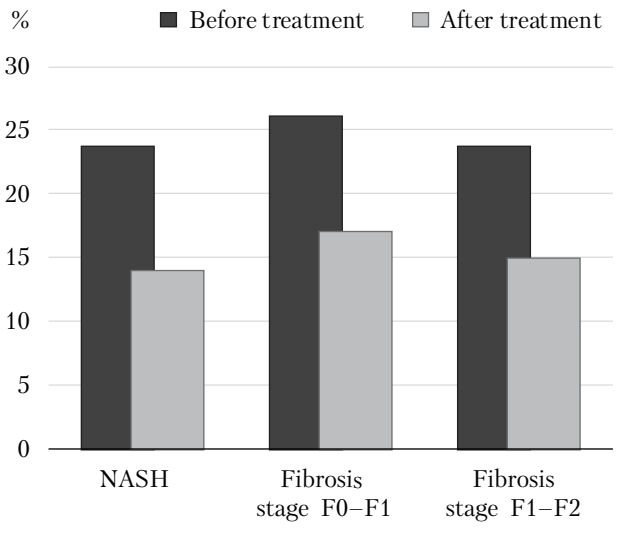

Figure 3. Results of SAMe and antihypertensive combination treatment on the NASH and LF stages in patients with MASLD and AH

diminished increases in serum transaminase activities and ameliorated prooxidant-antioxidant balance. Histopathological scores for hepatic steatosis, inflammation, and fibrosis were decreased by SAMe treatment [3]. These data are also consistent with our study findings. According to our results, SAMe has pronounced cytoprotective, anti-inflammatory, and antifibrotic effects.

Conclusions

The results of SAMe and antihypertensive combination therapy show the improvement of the clinical course of the disease, liver function, and the regression of the LF stage. Therefore, the inclusion of SAMe in standard antihypertensive therapy is an appropriate method of treatment of patients with comorbid course of MASLD and AH as a pathogenetic drug with a pronounced cytoprotective, anti-inflammatory and antifibrotic effect.

Limitations. The findings obtained are not representative of all subjects with MASLD because of the small sample size and the strict inclusion criteria. Further prospective studies should be arranged to find effective treatments for reducing oncological and cardiovascular risks for patients with MASLD and AH comorbid course.

Conflicts of interest: none. This study did not receive external funding.

Authorship contributions: conception and design, critical revision of the article — N. M. Z., K. O. P.; acquisition of data — T. M. A., V. I. M., G. Y. P., M. O. V., D. V. M.; analysis, and interpretation of data, drafting the article — T. M. A., K. O. P., V. I. M., M. O. V., D. V. M.

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Клінічна ефективність S-аденозил-L-метіоніну та комбінованого антигіпертензивного лікування в пацієнтів із коморбідним перебігом метаболічно-асоційованої стеатотичної хвороби печінки й артеріальної гіпертензії

Мета — визначити ймовірний вплив S-аденозил-L-метіоніну (SAMe) та комбінованої антигіпертензивної терапії на клінічний перебіг захворювання, ферментативну активність печінки (рівень аспартатамінотрансферази, аланінамінотрансферази, γ-глутамілтранспептидази, лужної фосфатази), активність неалкогольного стеатогепатиту) та стадію фіброзу печінки (ФП) у пацієнтів із коморбідним перебігом метаболічно-асоційованої стеатотичної хвороби печінки (МАСХП) і артеріальної гіпертензії (АГ).

Матеріали та методи. Обстежено 40 пацієнтів із коморбідним перебігом МАСХП і АГ до та після лікування SAMe й комбінованою антигіпертензивною терапією тривалістю 5 міс. У контрольну групу залучено 20 практично здорових осіб. Пацієнти з вірусним гепатитом, цирозом печінки, алкогольною хворобою печінки, АГ III стадії та ФП F3—4 були вилучені з дослідження. Вивчення показників цитолізу печінки проводили за допомогою біохімічних методів. Виразність ФП оцінювали за результатами транзиторної еластографії.

Результати. Аналіз застосування SAMe та комбінованої антигіпертензивної терапії у хворих на МАСХП і АГ виявив статистично значуще поліпшення клінічного перебігу захворювання (зменшення скарг на підвищену втомлюваність, головний біль, загальну слабкість, біль у правому підребер'ї, порушення сну та погіршення настрою ($p < 0,05$)), зниження систолічного артеріального тиску ($p < 0,01$), діастолічного артеріального тиску ($p < 0,05$), індексу маси тіла ($p < 0,05$), величини співвідношення обводу талії до обводу стегон ($p = 0,05$), рівня таких показників цитолізу печінки, як аспартатамінотрансферази ($p < 0,01$), аланінамінотрансферази ($p < 0,01$), γ-глутамілтранспептидази ($p < 0,01$), лужної фосфатази ($p < 0,05$). Також установлено зниження активності неалкогольного стеатогепатиту ($p < 0,05$) і регрес стадії ФП ($p < 0,05$).

Висновки. Результати застосування SAMe та комбінованої антигіпертензивної терапії свідчать про поліпшення клінічного перебігу захворювання, функції печінки та регрес стадії ФП. Використання SAMe як патогенетичного препарату з виразною цитопротекторною, протизапальною й антифібротичною дією є доцільним у стандартній комбінованій терапії пацієнтів із МАСХП і АГ.

Ключові слова: метаболічно-асоційована стеатотична хвороба печінки, артеріальна гіпертензія, фіброз печінки, неалкогольний стеатогепатит, S-аденозил-L-метіонін.

ДЛЯ ЦИТУВАННЯ

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