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OPPORTUNITIES FOR THE USE OF NATURAL AND PREFORMED PHYSICAL FACTORS IN THE COMPLEX TREATMENT OF PATIENTS WITH CHRONIC VIRAL HEPATITIS C WITH ASSOCIATED NON-ALCOHOLIC FATTY LIVER DISEASE

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Abstract

One of the urgent problems of modern hepatology remains the treatment of patients with chronic viral hepatitis C, which is associated with an increase in the incidence and development of complications - cirrhosis of the liver and hepatocellular carcinoma. The presence of non-alcoholic fatty liver disease in patients accelerates the progression rate of HCV infection and reduces the effectiveness and tolerability of antiviral therapy. The above circumstances initiated us to the search for new non-drug technologies for the treatment of this category of patients. The work aimed to evaluate the effectiveness of the integrated use of standard antiviral therapy, drinking silicon low-mineralized sodium bicarbonate mineral water, and EHF-therapy in patients with chronic viral hepatitis C with concomitant non-alcoholic fatty liver disease. We used the following methods: anamnestic, general clinical, biochemical, serological, immunological, Ultrasonographic examination of the digestive organs. We examined 42 patients who were divided into two groups. The control group (22 people) received the basic treatment complex, which included dietary nutrition, standard antiviral therapy for 12 months, and an internal intake of mineral water during the first month

of treatment. The main group (20 people), in addition to the basic complex of treatment, additionally received EHF-therapy procedures for three months. Evaluation of the effectiveness of treatment was carried out after 1 and 3 months from the start of treatment. The treatment was accompanied by the positive dynamics of most signs of the disease in both groups, with a predominance of EHF-therapy. In patients of main group, the disappearance of complications of antiviral therapy was established - the absence of cytopenic syndrome, normalization of immunological status, stimulation of interferonogenesis, restoration of equilibrium in the lipid peroxidation system and antioxidant system. These positive results made it possible to complete the course of therapy for all patients and obtain a virological response in 50% of patients.

Keywords: chronic viral hepatitis C; non-alcoholic fatty liver disease; mineral water; EHF-therapy.

Introduction

Chronic viral hepatitis C (CVH) remains an urgent medical and social problem of the healthcare system worldwide, due to its prevalence (more than 3% of the world's population), and a high risk of liver cirrhosis and hepatocellular carcinoma [1, 2]. According to various studies, liver steatosis is observed in almost 50% of patients infected with hepatitis C.

The possibility of developing non-alcoholic fatty liver disease (NAFLD) in chronic HCV infection is significantly higher than in other liver diseases. It is diagnosed two times more often than in chronic HBV infection and autoimmune hepatitis [3, 4, 5]. The presence of fatty liver in patients with chronic hepatitis C increases the rate of progression of HCV infection and reduces the effectiveness of antiviral therapy (AVT).

Our scientific research began in 2011 when the “gold standard” for treating patients with chronic hepatitis C was the use of linear or pegylated interferons in combination with ribavirin. The effectiveness of such treatment, that is, the achievement of a stable virologic response (SVR), ranged from 40 to 60%. Meanwhile, such therapy had a large number of contraindications and several significant drawbacks, namely, the development of severe side effects. Also, the lack of effectiveness and high cost of treatment forced some patients to terminate the AVT prematurely or to not agree to such treatment at all [6, 7].

The above circumstances initiated us to the search and development of new non-drug methods of treatment of patients with chronic hepatitis C with chronic concomitant NAFLD to increase the effectiveness of therapy and improve the quality of life of patients.

Unfortunately, the literature almost does not consider the possibility of using natural and preformed physical factors in the treatment of patients of this category, despite the extensive experience of Ukrainian scientists in their use [8, 9].

That is why the use of natural and preformed factors in the complex treatment of patients with chronic hepatitis C with chronic concomitant NAFLD may be one of the ways to increase the effectiveness of therapy, eliminating the complications of drug treatment.

The purpose of the work is to evaluate the effectiveness of the integrated use of standard AVT, drinking water of low-mineralized silicon sodium hydrogen mineral water, and EHF-therapy in patients with chronic hepatitis C with concomitant NAFLD.

Materials and methods

We examined 42 patients with chronic hepatitis C (genotype 1b in the replication phase, minimal and moderate degree of activity) with concomitant NAFLD. Patients were in the clinic of rehabilitation treatment of patients with a gastroenterological profile of the State Institution “Ukrainian Research Institute of Medical Rehabilitation and Balneology of the Ministry of Health of Ukraine”.

The study used methods such as anamnestic, clinical (gastroenterological examination in which the severity of pain, dyspeptic, asthenic syndromes was assessed based on the review of subjective and objective signs of the disease), paraclinical methods (included studies of a general clinical, biochemical research of blood parameters, determination of the NOMA index, HCV RNA PCR (qualitative and quantitative determination of viral load, genotyping), study indicators antioxidant system (AOS) and lipid peroxidation (LPO), quantitative determination of endogenous interferon-alpha (IFN- α) in blood serum, immunological blood tests, ultrasonographic studies of abdominal organs, statistical methods.

Before treatment, we formed two groups of 42 patients. The age of patients ranged from 23 to 55 years and averaged $(42.15 \pm 10.23)\%$ of years. The sex ratio was as follows: women $(61.91 \pm 7.49)\%$, and men $(38.09 \pm 7.49)\%$ of the examined. The concomitant pathology of the digestive organs in patients with chronic hepatitis C was mainly represented by diseases of the pancreatobiliary system. In essence, chronic non-calculous cholecystitis was diagnosed in $(64.29 \pm 7.39)\%$ of the examined, and chronic pancreatitis in $(45.24 \pm 7.68)\%$ of patients. A third of the patients suffered from chronic gastritis.

The first group of patients (22 people) took the basic treatment complex - diet No. 5, which corresponds to the Mediterranean diet [10], standard AVT (interferon-alpha - 2 b and ribavirin) for 12 months and internal intake of mineral water (MW) for the first months of treatment.

The prerequisite for our choice regarding the use of MW in the complex treatment of patients with chronic hepatitis C with concomitant NAFLD was the availability of data on the insulinotropic, lipid-lowering, atherogenic, cardioprotective properties of MV with an active content of macro components: bicarbonates, sulfates, sodium, potassium, magnesium and trace elements (silicon, iron, etc.).) These properties are pathogenetically substantiated in the treatment of this category of patients [11, 12, 13]. The authors provide data on the violation of the metabolism of trace elements in NAFLD and indicate the possibility of their therapeutic appointment for patients NAFLD [14, 15].

We used packaged silicon low-mineralized bicarbonate sodium water of well No. 242, the village of Shayan, Khust district of the Transcarpathian region (Ukraine). The total mineralization of MW was 1.86 g / l. The main anions in the chemical composition of MW were HCO_3^- (1.187 g / l), Cl^- (0.095 g / l), and among the cations, Na^+ and K^+ ions (0.447 g / l). Other cations and anions - SO_4^{2-} (0.059 g / l), Ca^{2+} (0.064 g / l) and Mg^{2+} (0.008 g / l) had insignificant concentrations. In MW, there are biologically active components and compounds that are standardized in balneology according to the legislation of Ukraine (12), and add specific properties to waters. Such components are H_2SiO_3 (metasilicic acid) - 69.42 mg / l (silicones are considered MW with an H_2SiO_3 content of 50 mg / l and H_3BO_3 (Orthoboric acid) - 15.83 mg / l (boric ones are MW with an H_3BO_3 content from 35 mg / l).

The second group of patients (20 people), in addition to the basic treatment, received EHF-therapy procedures ((within 3 months according to the scheme developed by us). From physiotherapeutic methods of treatment, we chose EHF-therapy, which has a systemic character of influence on the body, by exposure to electromagnetic waves in the noise range (30-300 GHz) and low intensity (up to 10 mW / cm^2) on bilayer cell membranes, resulting in there is an acute-resonance effect of pathological oscillations and restoration of the cell signal to typical biophysical values. Due to this, the main therapeutic effects of EHF-therapy are achieved: immunomodulating, detoxifying, analgesic, anti-stress, anti-inflammatory, regenerating.

The inclusion of EHF-therapy procedures in complex treatment allowed to reduce the dosage and complications of drug therapy, to improve the quality of medicine in pharmacoresistant patients, for whom EHF-therapy is sometimes the treatment of choice [16, 17].

Assessment of the effectiveness of treatment was carried out after 1 and 3 months from the start of treatment. Statistical processing of the obtained data was carried out using the programs for biomedical research, Microsoft Exel 2010 and Statistica 6.0 (StatSoft, 2006).

The average values are given in the form ($M \pm m$), where M is the average value of the indicator, m is the standard error of the mean. Significant changes were considered to be those that were within the bounds of reliability according to Student's tables.

Results and discussion

Before treatment, the manifestations of astheno-vegetative ($88.09 \pm 4.99\%$), pain abdominal ($59.52 \pm 7.57\%$), dyspeptic ($54.76 \pm 7.68\%$) syndromes prevailed in patients. Significantly less often, patients complained of arthralgia ($28.57 \pm 6.97\%$) of the examined.

An objective examination most often determined pain on palpation in the right hypochondrium ($47.61 \pm 7.70\%$) and hepatomegaly ($57.14 \pm 7.64\%$) of patients.

A complete blood count revealed signs of hypochromic anemia in ($11.90 \pm 4.99\%$), leukocytopenia in ($7.14 \pm 3.97\%$), thrombocytopenia in ($4.76 \pm 3.28\%$) of the examined. In ($14.28 \pm 5.39\%$) of patients, there was an increase in ESR level. A biochemical blood test before treatment revealed impaired liver function in most patients. In the examined patients, the signs of cytolytic ($64.28 \pm 7.39\%$) and cholestatic ($42.86 \pm 7.64\%$) of syndromes dominated, in ($47.62 \pm 7.71\%$) of the examined, the level of thymol test was increased.

Signs of dyslipidemia were observed in all patients. They were characterized by an increase in the level of total cholesterol (OH) to an average of (6.83 ± 0.19) mmol / L, and the level of triglycerides - to (2.14 ± 0.14) mmol / L. The value of LDL increased on average to (4.05 ± 0.28) mmol / L, the level of high-density lipoproteins (HDL) decreased on average to (1.52 ± 0.16) mmol / L. As a result, the atherogenic coefficient averaged (4.58 ± 0.32) units. The plasma glucose level was on average (6.51 ± 0.39) mmol / L, insulin concentration was slightly increased and averaged (18.64 ± 0.97) $\mu\text{U} / \text{ml}$. Moreover, the HOMA index was (5.38 ± 0.43) units, which indicates a pronounced insulin resistance in the examined patients.

A study of the state of LPO and AOS parameters in all patients with chronic hepatitis C with concomitant NAFLD revealed an increase in the level of diene conjugate (DC) and malondialdehyde (MDA) (average values were - (1.17 ± 0.06) unit and (6.37 ± 0.06) $\mu\text{mol} / \text{L}$, as well as a decrease in the index of total antioxidant activity.

The initial level of endogenous α -IFN was significantly reduced in all examined; the average value was (1.47 ± 0.24) pkg/ml.

The study of blood immunological parameters in all examined before treatment revealed a decrease in the level of CD3 and CD4 - lymphocytes and phagocyte activity in ($76.19 \pm 6.57\%$) of patients, as well as an increase in the level of circulating immune complexes (CEC) in ($71.42 \pm 6.97\%$) of patients.

According to ultrasound, 100% of the patients had sonographic features of liver steatosis (distal attenuation of the echo signal, fuzzy vascular pattern, diffuse increase in the "brightness" of the liver parenchyma).

In 27 patients ($64.28 \pm 7.39\%$), hepatomegaly was determined, in 38 patients ($90.47 \pm 4.52\%$), an increase in liver echogenicity was detected. The liver structure was fine-grained in more than half of the examined ($54.76 \pm 7.68\%$). In ($64.29 \pm 7.39\%$) of patients, the presence of inhomogeneous contents in the gallbladder was observed, against the background of thickening and compaction of its walls. Uneven and fuzzy contours of the pancreas, changes in its echogenicity, and heterogeneity of the echostructure were observed in ($45.24 \pm 7.68\%$) of the examined.

Analysis of the results obtained one month after the start of therapy showed the advantage of complex treatment using EHF-therapy procedures.

A significant decrease in the manifestations of the pain of abdominal, dyspeptic, astheno-vegetative syndromes in patients of group II ($p < 0.05$), in contrast to patients of group I, where there was no similar dynamics ($p > 0.05$), was noted. The general blood test determined the presence of leuko- and thrombocytopenia in ($54.54 \pm 10.61\%$) and ($40.91 \pm 10.48\%$) of patients of group I, respectively. In patients of group II, leukopenia was observed only in ($35.00 \pm 10.66\%$) of patients, and thrombocytopenia in ($20.00 \pm 8.94\%$) of patients. Significant changes in the functional state of the liver and immunological parameters of blood in patients of both groups were not observed. Also, in the majority of the examined, there was no reliable normalization of the LP and AOS parameters; however, in patients of group II, there was a definite tendency to normalize these indicators ($p > 0.05$).

The study of the level of endogenous α -IFN showed a pronounced stimulating effect of EHF-therapy after one month of treatment. The level of α -IFN was normalized in ($80.95 \pm 6.06\%$) of patients of the main group ($p < 0.05$), compared with patients in the control group, where normalization of interferonogenesis was observed in ($61.91 \pm 7.49\%$) of cases. A quick virological response (according to PCR) was obtained in ($30.00 \pm 10.25\%$) of patients of group II and ($27.27 \pm 9.49\%$) of patients of group I.

According to ultrasound, one month after the start of therapy, there was no significant decrease in liver size and signs of an inflammatory process in the hepatopancreatobiliary system in both groups.

Evaluation of the results of therapy after three months showed the absence of manifestations of asthenic, pain abdominal, arthralgic syndromes in most patients of both

groups. Along with this, only in patients of group II the significant ($p < 0.003$) leveling of complaints of the dyspeptic syndrome was determined.

The study of a general blood test showed a further increase in cytopenic syndrome in group I (leukopenia - $(59.09 \pm 10.48)\%$ and thrombocytopenia - $(45.45 \pm 10.62)\%$ of the examined), in contrast to patients of group II, where indicators hemograms practically did not change (leukopenia - $(35.00 \pm 10.66)\%$ and thrombocytopenia $(25.00 \pm 9.68\%$ of patients).

In patients of both groups, a significant improvement ($p < 0.05$) of liver function tests was observed. In patients of both groups during the entire course of treatment, there was a significant dynamics of a decrease in the concentration of total cholesterol and LDL ($p < 0.05$), other indicators of the lipid profile did not change.

Analysis of carbohydrate metabolism during all months of treatment showed a decrease in insulin resistance, including due to hyperinsulinemia. There was also a tendency to a decrease in serum glucose ($p > 0.05$), a significant decrease in insulin concentration ($p < 0.05$), primarily due to a decrease in hyperinsulinemia. As a result, the HOMA-IR index decreased ($p < 0.05$), although reference values could not be achieved.

In patients of group II, there was a significant ($p < 0.02$) normalization of most indicators of the immune status (CD3, CD4, active phagocytes), in contrast to patients of group I ($p > 0.5$).

Also, during these terms, normalization of the LPO and AOS system parameters was observed in all patients of group II ($p < 0.05$). This effect did not occur in patients of the control group, where the predominance of LPO processes over the antioxidant defense system was observed. An early virological response was obtained in $(13.64 \pm 7.32)\%$ of patients of group I and $(20.00 \pm 8.94)\%$ of patients of group II.

Analysis of ultrasound data after three months from the start of treatment showed that the improvement of ultrasonographic characteristics of the digestive system was more pronounced in group II. In most patients, along with the restoration of echogenicity and normalization of liver size, improved penetration of the echo signal into its deeper layers, the appearance of a homogeneous content in the gall bladder was observed. In patients of the first group, restoration of echogenicity of the liver was observed in half of the cases, a tendency ($p > 0.05$) to a decrease in its size was determined; however, inflammatory changes in the gallbladder and pancreas persisted.

Thus, the proposed methods can be used in the complex treatment of patients with chronic hepatitis C with concomitant NAFLD to reduce the incidence of complications from AVT, stimulate interferonogenesis, normalize the immunological status, restore the LPO and

AOS systems, improve the functional state of the gallbladder and pancreas. The application of the proposed methods increases the effectiveness of therapy and helps to improve the quality of life of this category of patients.

Conclusions

1. In patients with chronic hepatitis C with concomitant NAFLD (genotype 1b, replication phase), the clinical signs of asthenic (88.09%) and pain abdominal (59.52%) syndromes, impaired liver function (cytolytic (64.28%), mesenchymal-inflammatory (47.62%), cholestatic (42.86%) syndromes). The presence of insulin resistance, a decrease in the level of endogenous α -IFN, along with the predominance of the processes of free radical oxidation of lipids and a reduction in antioxidant activity, were determined in all examined patients.

2. The use of silicon low-mineralized hydrocarbonate sodium MW and standard AVT helps reduce the severity of astheno-vegetative and pain abdominal syndromes, normalize the functional state of the liver, and stimulate interferonogenesis. The virological response had obtained in 40.91% of patients in this group.

3. The mixed-use of MW, standard AVT, and EHF-therapy procedures helps to eliminate astheno-vegetative, pain abdominal, and dyspeptic syndromes, normalize the functional state of the liver and mitigate inflammatory changes in the pancreatobiliary system. Patients showed marked stimulation of interferonogenesis, normalization of immunological status, and restoration of equilibrium in the LPO and AOS systems. The virological response was obtained in 50.00% of patients in this group.

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