International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 9; Issue 06(B); June 2020; Page No.22458-22461
DOI: http://dx.doi.org/10.24327/ijcar.2020.22461.4430

Research Article

NEW OPPORTUNITIES FOR THE USE OF "DRY" CARBON DIOXIDE BATHS IN THE COMPLEX TREATMENT OF PATIENTS WITH CHRONIC VIRAL HEPATITIS WITH RELATED NON-ALCOHOLIC FATTY LIVER DISEASE

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A R T I C L E I N F O

Article History:
Received 6th March, 2020
Received in revised form 15th April, 2020
Accepted 12th May, 2020
Published online 28th June, 2020

Key words:

chronic viral hepatitis C, non-alcoholic fatty liver disease, antiviral therapy, "dry" carbon dioxide baths.

A B S T R A C T

An urgent problem of modern hepatology is the treatment of patients with chronic viral hepatitis C (CHC), which is associated with the prevalence of this disease in the world and the development of serious complications. The presence in these patients of concomitant non-alcoholic fatty liver disease (NAFLD) accelerates the progression rate of HCV infection and reduces the effectiveness of antiviral therapy (AVT). The purpose of the work is to evaluate the effectiveness of the use of a new treatment complex: conducting an AVT and dry carbon dioxide bath (DCDB) procedures in patients with chronic hepatitis C with concomitant NAFLD. Patients of the 1st group received the basic complex of treatment: diet therapy, dosed exercise regimen, AVT included sofosbuvir (400 mg), and ledipasvir (90 mg). Patients of 2 groups on the background of a similar basic therapy additionally received DCDB procedures - 3 series of procedures (10 procedures daily with a break of 20 days). Positive dynamics were established in both groups, but in patients of the 2nd group, it was possible to achieve faster elimination of asthenic and pain abdominal syndromes ($p < 0.05$) and normalize all indicators of the lipid profile ($p < 0.001$).

INTRODUCTION

Difficulties arising in the treatment of patients with chronic viral hepatitis C (CHC) are currently associated with the presence of concomitant liver disease in patients, namely, fatty degeneration of the liver, which contributes to the progression of HCV infection (Noureddin *et al*. 2018). In patients with chronic hepatitis C, two primary forms of steatosis of the liver (SL) are considered: the virus-induced and metabolic. Metabolic SL can be determined for all genotypes of the virus and most often develops in the presence of obesity, hyperlipidemia, impaired glucose tolerance (Kralj *et al*. 2016). The occurrence of metabolic steatosis is not directly related to the hepatitis C virus; however, liver pathology may be associated with an acceleration of fibrosis progression. Virus-induced SL can occur due to direct exposure to the virus; this applies mainly to the 3rd genotype. This type of joint venture also contributes to the rapid progression of the disease. Steatosis (regardless of its form - metabolic or virus-induced) worsens the prognosis of the rate of fibrosis in patients with chronic hepatitis C (Adinolfi *et al*. 2016; Ringehan *et al*. 2017).

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At present, the medical community all over the world associates the possibilities of treating patients with chronic hepatitis C with concomitant NAFLD only with the use of drugs, and insufficient attention is paid to the question of the appropriateness of additional use of physical methods of treatment in this category of patients (meaning balneological and physiotherapeutic methods). It should be remembered that physical treatment methods cannot replace the basic drug therapy of patients with chronic hepatitis C with concomitant NAFLD; they can supplement it. At the analysis of literature data, we drew attention to such a physiotherapeutic method as carbogenotherapy, namely, "dry" carbon dioxide baths (DCDB). DCDB is a method of the percutaneous therapeutic effect of carbon dioxide on a patient whose body is located up to the neck level in a special box. According to the current physical factor, the therapeutic use of S DCDB is attributed to carbogenotherapy, a type of treatment with carbon dioxide (carbon dioxide, CO_2), (Pianez *et al*. 2016). Carbon dioxide (CO_2) is an essential physiological factor that affects metabolism, redox processes in the cell, and hormonal regulation (Koutna 2011). Researchers note the positive effect of DCDB on lipid metabolism: lipid metabolism increases, cholesterol, and low-density lipoproteins decrease in patients with atherosclerosis, and the breakdown of fats and fat-like substances is enhanced (Suceveanu *et al*. 2015). The effect of carbon dioxide baths is also manifested in a change in the functional state of the higher parts of the central nervous and

autonomic systems due to the restoration of the balance of nervous processes (Ezhov *et al*. 2017). The increase in oxygen content in arterial blood is significant in the action of carbon dioxide baths, as a result of which tissues and organs receive a higher amount of oxygen, all metabolic processes in the body (carbohydrate, fat, protein, electrolyte) are strengthened and improved (Drogovoz *et al*. 2016).

Modern concepts of the mechanism of therapeutic action of carbon dioxide are considered to emphasis on its impact on patients with various pathologies treated with dry carbon dioxide baths while discussing further prospects for the practical application of this method (Persiianova-Dubrova *et al*. 2010; Pagourelias *et al*. al. 2011; Kołodziejczak *et al*. 2018).

Meanwhile, we have not found studies regarding the possibilities of using DCDB in the complex treatment of patients with chronic hepatitis C with concomitant NAFLD. We considered it appropriate to study the therapeutic effect of DCDB on the development of the clinical, biochemical, and virological response, as well as the regression of fibrosis. We first examined the impact of DCDB on the clinical course of main (CHC) and concomitant diseases (NAFLD), the functional state of the liver, especially the dynamics of lipid and carbohydrate metabolism, the frequency of elimination of hepatitis C virus, ultrasonographic signs of the inflammatory process in the liver, gall bladder, and pancreas.

That is why the work aimed to study the effectiveness of the integrated use of antiviral therapy (AVT) and dry carbon dioxide bath (DCDB) procedures in patients with chronic hepatitis C with concomitant NAFLD.

Methods Design. We examined 40 patients with chronic hepatitis C (genotype 1b in the replication phase, minimal and moderate activity) with concomitant NAFLD. They were monitored at the State Institution "Ukrainian Research Institute of Medical Rehabilitation and Balneology of the Ministry of Health of Ukraine ", Odessa, Ukraine. The research used methods such as anamnestic and clinical, conducted a study of general clinical, biochemical blood parameters, serological markers of viral hepatitis C, HCV PCR RNA (qualitative and quantitative determination, genotyping), ultrasonography of the digestive system, statistical methods.

We formed two groups of patients with chronic hepatitis C with concomitant NAFLD. Patients of group I (20 patients, control group) received a standard complex of treatment (diet therapy that corresponded to the Mediterranean diet, dosed physical activity regimen, antiviral therapy - sofosbuvir (400 mg) and ledipasvir (90 mg) for 3 months. Patients of group II (20 people, the main group) received additional DCDB procedures (daily ten procedures for the first month of treatment, a break of 20 days, ten procedures for the second month of treatment, a break of 20 days, ten procedures for the third month of therapy). Evaluation of the effectiveness of treatment was carried out after three 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 (Stat Soft, 2006). The average values are given in the form (M ± 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 confidence limits according to Student's tables <0.05.

RESULTS

The average age of patients was (48.12 ± 10.29) years. By gender, patients were distributed as follows: women - 23 ((57.50 ± 7.81)%) people, men - 17 ((42.50 ± 7.81)%) people. At the beginning of treatment, the overwhelming majority of patients ((82.50 ± 6.00)% of individuals) complained of an asthenic syndrome (general weakness, decreased working capacity, fatigue). Abdominal pain syndrome in the form of pain or severity in the right hypochondrium was detected in (55.00 ± 7.86)% of the examined. Manifestations of dyspeptic syndrome disturbed (47.50 ± 7.89)% of the respondents. An objective examination most often determined pain on palpation of the right hypochondrium - in (57.50 ± 7.81)% of the respondents, less often determined pain in the left hypochondrium - (40.00 ± 7.74)% of cases. Hepatomegaly, mainly due to the left lobe, was identified in (72.50 ± 7.06)% of patients. Before the start of treatment, an increase in the level of monocytes was determined in 29 (72.50 ± 7.40)% of patients in a general blood test, in 27 (67.50 ± 4.40)% of patients - an increase in the level of lymphocytes, in 21 (52.50 ± 7.89)% of people were diagnosed with an increase in the level of the erythrocyte sedimentation rate indicator (ESR). The average total blood count in the rest of the examined patients coincided with physiological norms. In (77.50 ± 6.60)% of patients, the study of biochemical blood parameters revealed a cytolytic syndrome. The presence of a mesenchymal inflammatory reaction in the liver, as evidenced by an increase in the level of thymol test, was found in 27 (67.50 ± 7.40) % of the examined individuals. In 21 (52.50 ± 7.89)% of patients, cholestasis was observed, characterized by an increase of 1.5 times the average level of alkaline phosphatase and gamma-glutamyl transpeptidase. In all examined patients, disorders of lipid metabolism in the form of hypercholesterolemia, hypertriglyceridemia, an increase in the atherogenicity coefficient, disorders of low-density lipoproteins (LDL) and high-density lipoproteins (HDL) were identified. An increase in the level of total cholesterol (TCH) was on average for all examined (6.89 ± 0.3 7) mmol / L, an increase in the level of LDL on average (4.48 ± 0.12) mmol / L, a decrease in the level of HDL on average in the group up to (1.13 ± 0.09) mmol / l. The atherogenic coefficient was on average (4.28 ± 0.21) units. The plasma glucose level averaged (6.47 ± 0.31) mmol / L, the insulin concentration was slightly increased and averaged (18.62 ± 0.87) μU / ml. At the same time, the NOMA index was (5.35 ± 0.42) units, indicating pronounced insulin resistance (IR) in the examined patients. In all patients with chronic hepatitis C with concomitant NAFLD, active replication of HCV infection in serum was determined by PCR. In 25 patients (62.50 ± 7.65)%, a low level of the virological load was diagnosed, and in 15 (37.50 ± 7.65)% of the examined patients a high level of virological load (> 800 000 IU / ml) was diagnosed. In all patients, genotype 1 b was determined. During ultrasound examination (ultrasound) of the abdominal organs, an increase in liver echogenicity and diffuse changes in its tissue of varying severity were observed in (80.00 ± 6.32) %% patients, which was accompanied by hepatomegaly in 72.50 ± 7.06)% person. Sonographic signs of steatosis of the liver (distal attenuation of the echo signal,

fuzzy vascular pattern, diffuse increase in the "brightness" of the hepatic parenchyma) were determined in all examined patients. Ultrasonographic signs of gallbladder pathology were noted in 22 (55.00 ± 7.86)%) patients, pancreas - in (42.00 ± 7.81)% of cases.

The treatment in both groups was accompanied by the positive dynamics of most of the signs of the disease; however, a detailed analysis revealed significant advantages in patients of the 2nd group. In patients of group 2, a significant decrease in the manifestations of asthenic ($p < 0.05$) and pain ($p < 0.05$) syndromes was established after one month from the start of therapy, which was not observed in patients of group 1, where significant changes were achieved only at the end treatment. As for dyspeptic syndrome, its positive dynamics was observed slowly and was presented by leveling some signs of dyspeptic syndrome only at the end of treatment ($p < 0.05$).

The study of indicators of a general blood test three months after the start of treatment revealed a reliable ($p < 0.001$) normalization of the ESR and lymphocyte levels in patients with an initially elevated level of these indicators. A significant ($p < 0.001$) decrease in the number of patients with monocytosis was also observed. Analysis of biochemical parameters determined reliable ($p < 0.05$) elimination of signs of cytolytic and cholestatic syndromes, normalization of the level of thymol test ($p < 0.05$) in patients of both groups at the end of three months of treatment. The normalization of lipid metabolism in patients of group 2 was established: a significant ($p < 0.001$) decrease in the concentration of TCH, the level of triglycerides, LDL, HDL, atherogenicity coefficient. In patients of group 1, only a tendency ($p > 0.05$) to decrease in the level of OX was determined. A study of the dynamics of carbohydrate metabolism in patients of both groups showed a slow dynamics in normalizing the HOMA-IR index (5.35 ± 0.42 at the beginning of treatment and 4.03 ± 0.32 at the end of treatment).

Analysis of the results of a study of the dynamics of the qualitative determination of HCV PCR RNA carried out after 1, 2 and 3 months from the start of treatment, showed the presence of virological response in all examined. At the end of treatment, there was an improvement in the ultrasound picture of the digestive system in all patients, namely: there was a tendency to a decrease in the acoustic density of the liver parenchyma, a reduction in the size of inflammatory foci, an improvement in the passage of the echo signal into the deep layers of the liver, and an improvement in the visualization of the vessels of the organ. A significant decrease in inflammatory signs in the gallbladder and pancreas was not found ($p > 0.5$).

A comparative analysis between patients of groups 1 and 2 indicates the overwhelming therapeutic effectiveness of the treatment complex with the addition of DCDB, which is determined by a decrease in the manifestations of asthenic ($p < 0.05$) and pain ($p < 0.05$) syndromes on the 30th day of treatment and achieving full normalization of lipid metabolism at the end of treatment.

Thus, the obtained results prove the advisability of using DCDB in the complex treatment of patients with chronic hepatitis C with concomitant NAFLD to restore lipid metabolism, improve ultrasonographic signs, i.e., influencing the main pathogenetic links in the formation and progression of NAFLD to increase the effectiveness of therapy for the underlying disease.

CONCLUSION

In patients with chronic hepatitis C with concomitant NAFLD, before the start of treatment, the clinical signs of asthenic (82.50%) and abdominal pain syndromes (55.00%) were most often determined, violations of the functional state of the liver: the presence of cytolytic (77.50%), mesenchymal and inflammatory (67.50%), cholestatic (52.50%) syndromes. All examined were diagnosed with signs of dyslipidemia and IR along with changes in ultrasound data - distal attenuation of the liver echo (100.0%) and hepatomegaly (72.50%).

Adding to the basic complex of the course of DCDB procedures in patients of group 2 leads to the speedy elimination of asthenic and pain abdominal syndromes, mesenchymal-inflammatory, cholestatic, cytolytic syndromes, normalization of all lipid profile parameters and causes a virological response in all patients of this group.

Conflict of Snterest: None.

Finansial : Assistance : None.

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How to cite this article:

Anna Izha, Natalia Dragomiretska, Iryna Zabolotna and Sergey Gushcha (2020) ' New Opportunities for the Use of "Dry" Carbon Dioxide Baths in the Complex Treatment of Patients with Chronic Viral Hepatitis With Related Non-Alcoholic Fatty Liver Disease', *International Journal of Current Advanced Research,* 09(06), pp. 22458-22461.
DOI: http://dx.doi.org/10.24327/ijcar.2020.22461.4430

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