INTERNATIONAL SEVEN JOURNAL
OF HEALTH RESEARCH
ISSN: 2764-9415

Hepatic encephalopathy approach: Pharmacological therapy

Abordagem da encefalopatia hepática: Terapia farmacológica

DOI: 10.56238/isevjhv2n5-032
Receipt of originals: 10/20/2023
Acceptance for publication: 11/08/2023

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ABSTRACT

Introduction: Hepatic encephalopathy is a neuropsychiatric complication that occurs in patients with advanced liver disease, resulting in a variety of neurological and psychiatric symptoms. Effective treatment is of paramount importance due to the morbidity associated with this condition. Objective: This study aims to review current therapeutic approaches for hepatic encephalopathy, highlighting common treatment strategies and future prospects for therapeutic intervention. Methodology: The review was conducted by searching scientific databases, including relevant clinical trials, to identify therapeutic strategies used in hepatic encephalopathy. Results: Common therapeutic approaches for hepatic encephalopathy include dietary protein restriction, the use of Lactulose for ammonia excretion, and the administration of antibiotics such as rifaximin to reduce ammonia-producing intestinal flora. Various research efforts are underway to discover future pharmacological therapies. Conclusion: The therapeutic approach to hepatic encephalopathy is multifaceted, aiming to alleviate acute symptoms and prevent recurrences. A multidisciplinary strategy is essential for the effective management of this complex condition, and ongoing research is exploring new therapies that may improve the prognosis and quality of life for affected patients. Understanding the pathophysiology of hepatic encephalopathy is evolving, offering hope for more effective treatments in the future.

Keywords: Hepatic encephalopathy, Drug therapy, Therapy.

1 INTRODUCTION

Hepatic Encephalopathy (HE) is a potentially reversible neuropsychiatric syndrome of metabolic origin, secondary to the accumulation of neurotoxic substances in brain tissue resulting from the complication of cirrhosis and acute liver diseases. Chronic liver failure is the main etiology of HS and is among the leading causes of death in Latin America. It has a slow course of evolution, usually around months, but may present periods of exacerbation. The clinical manifestations of the disease are heterogeneous, characterized mainly by changes in personality, consciousness, cognition and motor function. This disease compromises the patient's quality of life and significant expenses for health providers. (DANI, 2011; CIOGLIA; LIMA, 2019)

The normal liver is responsible for metabolizing and clarifying protein substances with neurotoxic potential, originating in the intestine. Under physiological conditions, toxins are absorbed by enterocytes, cells that line the intestinal mucosa, pass through the mesenteric circulation, reach the portal vein, and then penetrate the hepatic space to be metabolized. However, in patients with hepatocellular dysfunction and/or portal hypertension, due to failure to metabolize and/or divert blood from the mesenteric circulation to the systemic circulation, toxins reach brain tissue. (DANI, 2011; SAINTS; COSAC, 2020)

There are several ways to classify hepatic encephalopathy. According to the guidelines of the American Association for the Study of Liver Diseases (AASLD), according to the underlying cause, HS can be divided into three types: type A related to acute liver failure, type B as a consequence of the presence of portosystemic shunts in the absence of liver dysfunction, and type C related to the presence of portosystemic shunts with the presence of liver cirrhosis. Current discussions consider a fourth type (type D), defined as "acute-on-chronic liver failure" and characterized by acute deterioration of liver function in patients with chronic liver disease. (WEISSENBORN, 2019)

Regarding the clinical manifestations and the degree of impairment of the patient's autonomy, the disease can be divided into minimal or subclinical, mild (grade I) and severe (grade II, III, IV). As for the triggering factors, they can be divided into precipitate, when a causative factor is recognized, or non-precipitate, when this factor is not found. Finally, there is a temporal division classified as episodic, recurrent (when there are at least 2 episodes of HS in a period of 6 months) and persistent (presence of behavioral changes that are always present and negatively impact the patient's social life and behavior). Studies show that about 80% of patients with chronic

liver failure will develop minimal HS, which is considered an important predictive factor for the development of HS in the future. (CIOGLIA; LIMA, 2019; FERENCI, 2002)

Although it is a complex syndrome, there are still no studies that address the pathophysiological mechanisms in depth, which means that they have not been well elucidated. Among the existing suggestions are: neurotransmitter dysfunction, oxidative and nitrosative stress, hyperammonemia, and neuroinflammation. Currently, the neurotoxin that causes the disease is ammonia. (FRAZÃO et al., 2023; STRAUSS; REIS, 2011)

The symptoms observed are very broad, so the following can be mentioned in the semiological findings: mental confusion, personality changes, disorientation and impaired level of consciousness. The first symptoms to appear are usually sleep disturbances, such as changes in the sleep-wake cycle. Personality changes may be more frequent than when compared to psychiatric illnesses. The presence of asterixis (or "flapping tremor") can be detected, however, it is not pathognomonic of the disease. When HS results from liver cirrhosis, hepatic breath may also be present. In advanced stages, patients may progress to coma and, ultimately, death if they are not transplanted. (FRAZÃO et al., 2023; CIOGLIA; LIMA, 2019)

The diagnosis is eminently clinical and is based on a good anamnesis, consisting of the patient's history, physical examination, and evaluation of liver function. The existing complementary tests have some limitations, the serum ammonia dosage will be increased, but it has low specificity and the levels found cannot be related to the degree of encephalopathy. In addition, the electroencephalogram may demonstrate alterations, however, none of them are considered pathognomonic of HS, and they have no prognostic value. To assess severity, specific neurological scales and tests can be used, such as the Glasgow Coma Scale and the West Havens Scale for hepatic encephalopathy. Decompensating factors such as upper gastrointestinal bleeding, constipation, and infections should also be evaluated at the time of diagnosis. (SAINTS; COSAC, 2020)

The treatment is based on reducing the production of ammonia by the body, by controlling the proliferation of bacteria in the intestine and increasing the absorption of ammonia by the body. First-line therapy is based on Lactulose (beta-galactosidofructose), a compound that is metabolized by intestinal bacteria and transformed into organic acids capable of lowering enteric pH and preventing the production of ammonia-producing bacteria. (FALLAHZADEH; RAHIMI, 2022)

In patients with recurrent encephalopathy, therapy has been based on the use of non-absorbable antibiotics that act on intestinal bacteria, resulting in a decrease in ammonia production. Studies have shown that Rifaximin, the only antibiotic approved for use in HS, is able to act in the

patient's recovery and in the prevention of new conditions, so it can be used as an acute phase and maintenance treatment. (FALLAHZADEH; RAHIMI, 2022)

Other treatment options have been discussed, such as: L-ornithine-L-aspartate, capable of increasing the metabolism of ammonia into glutamine, but whose use is limited in case of severe renal failure. L-acetyl-carnitine has been pointed out as an option, since it acts by increasing the production of acetylcholine in the brain and improving the synthesis of proteins and phospholipids capable of alleviating neuronal toxicity in hepatic encephalopathy. In addition, the use of probiotics, sodium benzoate and oral zinc supplementation have been mentioned as therapeutic options. It is also worth emphasizing the importance of managing precipitating factors in the treatment of the condition and in the prevention of recurrences. (LANNA et al., 2011; FALLAHZADEH; RAHIMI, 2022)

2 OBJECTIVE

This study aims to address treatment options for Hepatic Encephalopathy, since it is a condition for which there are few approved therapies and several therapeutic options that are still in the process of development, thus requiring more studies to be done.

3 MATERIALS AND METHODS

The present study is an integrative literature review that enables the search, critical evaluation and synthesis of available evidence on the investigated topic. In the first stage, the following guiding question was asked: "What are the treatment options for Hepatic Encephalopathy?".

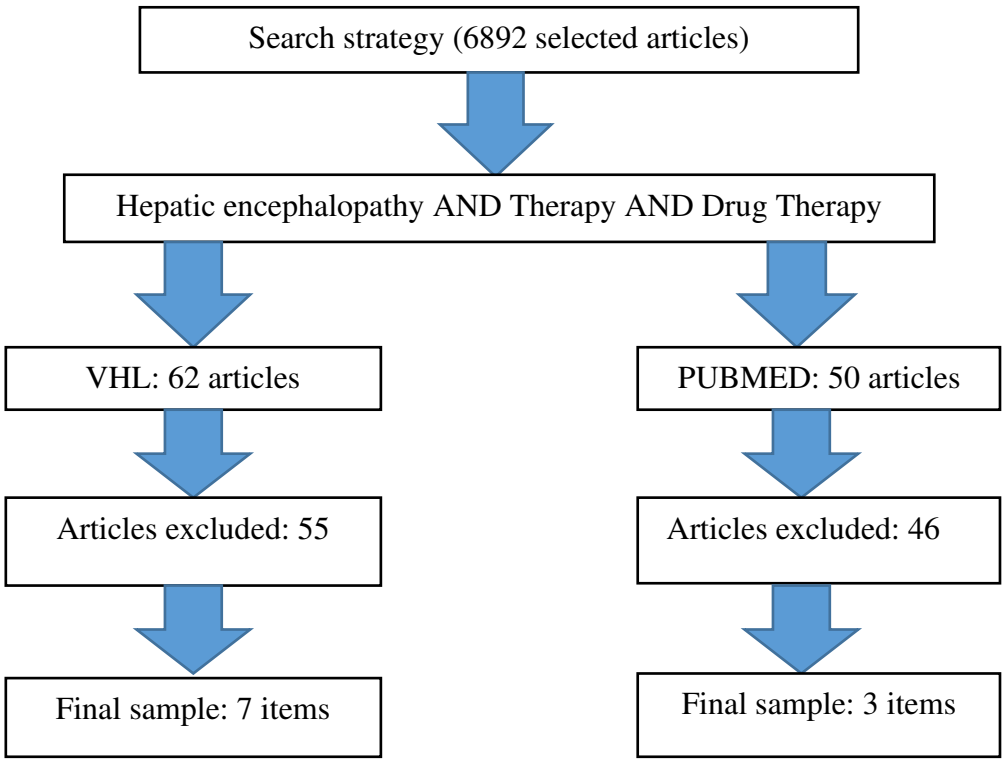
Then, in the second stage, in October 2023, the scientific search was carried out through the PubMed and VHL platforms, using the following descriptors indexed in the Health Sciences Descriptors (DeCS): 'hepatic encephalopathy'', 'therapy' and "*drug therapy*'', which were gathered using the Boolean descriptor AND.

Regarding the inclusion criteria for the selection of articles, the following were established: articles published in the last five years, available as full text and in English, Portuguese or Spanish.

Initially, 6892 studies were found based on the use of the descriptors in the databases, 35 in PubMed, 6702 in Medline, 21 in the Latin American and Caribbean Health Sciences Literature (LILACS), 14 in the Index Medicus for the Western Pacific (WPRIM), 6 in the Spanish Bibliographic Index in Health Sciences (IBECS), 1 in the National Bibliography in Health Sciences (BINACIS) and 1 in the Regional Base of Reports on the Evaluation of Technologies in

Salud de las Américas (BRISA/RedTESA). After applying the inclusion and exclusion criteria, 112 studies were selected; these were screened considering the reading of the title and keywords, and 23 studies were considered in the next stage of selection. Then, 4 were excluded due to duplication, leaving 19 papers to be read and, of these, 15 underwent a full analysis and 10 investigations made up the final sample.

Flowchart of the applied search strategy (n = 6892)



Finally, a data collection form was used for the critical analysis of the studies, consisting of the following information: title, authors, year, place of execution of the study, sample, objective, design, and main results (Pinheiro *et al.*, 2021). The selection of articles was carried out independently by three authors and there was no disagreement regarding the selected works.

4 RESULTS

The studies analyzed were published between 2018 and 2023 and conducted in the United States, England, India, Israel, Australia, Switzerland, Denmark, Ukraine, Russia, Poland, Hungary, Egypt, and China. Regarding the methodological approach, the studies were non-randomized clinical trials (n=1, 10%) and randomized clinical trials (n=9, 90%). Adults with a diagnosis of liver cirrhosis established by criteria such as Child-Phug, whether or not they had a history of hepatic encephalopathy participated in the studies (Chart 1).

Table 1 – Characteristics of the selected studies. (n=10).

Author and year	Outline	Objective	Sample & Scenario	Main results
PATEL et al., 2021	Randomized, double-blind, placebo-controlled clinical trial.	To examine the mechanism of action of Rifaximin, considered an effective treatment for Hepatic Encephalopathy	This was a randomized clinical trial with a duration of 17 months, with a double-blind placebo-controlled period of 90 days. The sample consisted of 50 patients with liver cirrhosis and chronic hepatic encephalopathy. Rifaximin was administered 550mg twice a day in one group and placebo in another group.	Rifaximin led to resolution of covert and apparent hepatic encephalopathy, reduced the likelihood of infection, reduced bowel oralization, and attenuated systemic inflammation.
FAGN et al., 2023	Randomized, double-blind, placebo-controlled clinical trial	To determine the impact of albumin vs. saline on minimal hepatic encephalopathy and quality of life in individuals with a history of hepatic encephalopathy who are already on treatment.	Randomized clinical trial with a 5-week double-blind period. The sample consisted of patients with cirrhosis and a history of hepatic encephalopathy, who had minimal hepatic encephalopathy and hypoalbuminemia already being treated for HS. Patients who were already receiving regular infusions of IV albumin were excluded. A weekly infusion of 25% IV albumin at a dose of 1.5g/kg was administered in one group and placebo and saline solution in another group.	Albumin infusions have been associated with improved cognitive function and quality of life, probably due to improved endothelial dysfunction.
BAJAJ et al., 2019	Randomized, placebo-controlled clinical trial.	To determine the safety, tolerability, and microbiota impact of mucosa and/or feces after fecal microbiota transplantation by oral capsules and their influence on brain function in hepatic encephalopathy.	Randomized placebo-controlled clinical trial lasting 5 weeks. The sample consisted of 20 patients with liver cirrhosis and recurrent hepatic encephalopathy using lactulose and rifaximin. A total of 15 fecal microbiota transplant capsules composed of feces from the same donor and placebo were administered to another group.	Administration of fecal microbiota transplantation orally was associated with a favorable change in mucosal and faecal microbial composition and an increase in the intestinal barrier.

AHMED et al., 2020	Randomized clinical trial	To compare the difference in efficacy and outcome of PEG+Lactulose administration versus Lactulose alone in acute-on-chronic-liver failure.	Randomized clinical trial. The sample consisted of 60 patients with acute-on-chronic liver failure with EH≥ grade 2 according to the West Haven criteria. Patients using Rifaximin were excluded. It was administered PEG3350+Lactulose in a group of 29 patients and Lactulose alone in another group of 31 patients.	PEG resulted in early and sustained resolution of hepatic encephalopathy with improved short-term survival. It has been shown to be a safe drug in patients with acute HS in the ACLF.
RAHIMI et al., 2021	Randomized, double-blind, placebo-controlled clinical trial.	To evaluate the efficacy and safety of Ornithine Phenylacetate (OP) in hospitalized patients with cirrhosis, increased ammonia levels at screening, and acute or overt hepatic encephalopathy.	This is a randomized phase I clinical trial with a duration of 35 months, with a double-blind placebo-controlled period of 5 days. Sample consisted of 231 hospitalized patients with liver cirrhosis, hyperammonemia, and stage 2 or higher hepatic encephalopathy in the Hepatic Encephalopathy Stage Tool (HEST). Continuous intravenous infusion of OP was administered for 5 days or less at a dose of 500ml/24h (20.8ml/h) + institution-standard drug in one group and placebo + institution-standard drug in another group.	The median time to clinical improvement based on ammonia measurements in local laboratories showed no significant difference between the groups. Analyses performed in a central laboratory based on ammonia levels demonstrated clinical improvement with an average of approximately 21 hours earlier in the OP group.
SAFADI et al., 2022	Randomized, double-blind, placebo-controlled clinical trial.	To analyze the pharmacokinetic and pharmacodynamic effects of Ornithine Phenylacetate (OP) in patients with hepatic encephalopathy and to evaluate the clinical effect of plasma reduction of ammonia concentration at the HS stage.	This is a randomized phase II clinical trial with a duration of 35 months, with a double-blind placebo-controlled period of 5 days. Sample consisted of 231 patients hospitalized with liver cirrhosis, hyperammonemia, and hepatic encephalopathy stage 2 or higher on the	The results of the pharmacokinetic/pharmacodynamic analysis are consistent with the purported mechanism of action of Ornithine Phenylacetate. Plasma OP levels reach steady state in approximately 48-72 hours, regardless of dose, and appear to increase as hepatic

			Hepatic Encephalopathy Stage Tool (HEST) despite standard of care care treatment for 48 hours. Continuous intravenous infusion of OP was administered for 5 days or less at a dose of 500ml/24h (20.8ml/h) + institution-standard drug in one group and placebo + institution-standard drug in another group.	function declines. Treatment with OP significantly improves plasma ammonia and the clinical stage of hepatic encephalopathy.
MONTAGNESE et al., 2021	Randomized, double-blind, placebo-controlled clinical trial.	To analyze data on the safety, pharmacokinetics (PK), and efficacy of golexanolone in adult patients with cirrhosis of the liver.	Randomized clinical trial with a 3-week double-blind placebo-controlled period. Sample consisted of 45 patients with Child-Pug A/B liver cirrhosis and abnormal continuous reaction time (CRT) at screening. Golaxenolone (10, 40 or 80 mg) was administered twice daily in one group and placebo in the other group.	Golexanolonone exhibited satisfactory safety and PK, being well tolerated and associated with improved cognitive performance. These results imply the relationship of GABA-A receptor modulating neurosteroids in the pathogenesis of hepatic encephalopathy, supporting the therapeutic potential of Golexanolon.
VIDOT et al., 2019	Randomized, double-blind, placebo-controlled clinical trial	To investigate the effect of oral supplementation with synbiotics and/or BCAAs on hepatic encephalopathy in patients who were receiving continuous treatment with Lactulose.	Randomized clinical trial with a double-blind placebo-controlled period of 8 weeks. Sample consisted of 49 patients with liver cirrhosis and a history of hepatic encephalopathy, who were on daily lactulosis, abstinence from alcohol and intravenous drugs for at least 3 months prior to study entry. The study was divided into 4 groups. Synbiotic placebo and BCAA placebo were administered in group 1, synbiotic + BCAA placebo in group 2, BCAA + synbiotic	Results suggest that oral supplementation with a combination of synbiotics and BCAAs in hepatic encephalopathy may be an effective additional treatment, however, there was a cognitive improvement with no change in ammonia levels.

			placebo in group 3, and synbiotic + BCAA in group 4.	
SHEHATA et al., 2018	Randomized clinical trial	To evaluate the safety and efficacy of Polyethylene Glycol (PEG) versus Lactulose in the management of hepatic encephalopathy.	Randomized clinical trial lasting 7 months. Sample consisted of 100 patients with liver cirrhosis after hepatitis C who were admitted with hepatic encephalopathy. Lactulose was administered to a group of 50 people and PEG to another group of 50 people.	Both Lactulose and PEG have been safe in the treatment of hepatic encephalopathy (HE). PEG significantly reduced the time required for HS treatment, reducing the length of hospital stay.
YU et al., 2022	**Clinical Trial**	**To evaluate the impact of Rifaximin administration on the gut microbiota and bacterial resistance profile in cirrhotic patients.**	**Clinical trial. A sample of 21 patients with cirrhosis who were in remission of recurrent hepatic encephalopathy received rifaximin 400mg three times a day for 12 weeks.**	**Rifaximin improved hyperammonemia and cognitive function in the 21 patients. The observations showed that the diversity of the gut microbiota, the composition and number of resistance genes, plasmids and insertion sequences did not change significantly.**

5 DISCUSSION

Advanced cirrhosis brings with it a number of complications, including hepatic encephalopathy (HE), variceal bleeding, ascites, and a propensity to develop infections. In addition to the above, cirrhosis causes an alteration in the intestinal microbiota, favoring the proliferation of ammonia-producing inflammatory bacteria species, and an increase in intestinal biomarkers of systemic inflammation, such as TNF-α and TLR-4. Although there are other factors related to the development of HS, hyperammonemia is the main cause associated with the occurrence of hepatic encephalopathy and its control is directly related to the main medical therapies approved by medical institutions, such as the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver.

Among the existing and currently recommended treatments is the antimicrobial Rifaximin-α. In a randomized placebo-controlled study to analyze the mechanism of action of rifaximin in improving HS, it was shown that the drug was associated with a reduction in the levels of gut-derived biomarkers of systemic inflammation. The antimicrobial suppressed the growth of opportunistic oral pathogens and led to an increase in oral health-associated levels of Lactobacillus

and Streptococcus spp. In addition, rifaximin was able to prevent cases of HS by improving the function of the intestinal barrier, by promoting the proliferation of epithelial cells and the production of mucus. Plasma lactate levels were also reduced by the drug. Considering that more than 75,000 microbial genes differ between patients with cirrhosis and healthy individuals, and that more than 50% of bacteria originate from saliva, it is clear that the drug mentioned is effective in hepatic encephalopathy and is related to an improvement in the patient's neurocognitive function. (PATEL et al., 2021)

Constant use of antimicrobials can lead to the development of bacterial resistance. Following this bias, a study by YU et al., 2022 sought to analyze the impact of Rifaximin on the gut microbiota and resistance profile in cirrhotic patients. The results found corroborated the findings of the study by PATEL et al., 2021, demonstrating that the drug had little effect on the diversity of the gut microbiota, increased the production of F. prusnitzii, a strain that produces anti-inflammatory effects that significantly improve intestinal inflammation and control obesity, as well as reducing bacteria associated with damage to the intestinal barrier and maintaining the abundance of beneficial bacteria. Regarding the development of resistance, the research did not observe a significant increase in intestinal resistance genes in patients, and there was no significant increase in plasmids and insertion sequences related to the transport and transmission of resistance-related genes, showing safety in the constant use of Rifaximin. However, it is worth noting that the research time was only 12 weeks, raising questions about resistance over longer periods. In addition, the sample size was small (n=21) and did not take into account intrinsic factors of each patient, such as diet, lifestyle, use of other medications, life history and genetics.

Among the consequences of hepatic encephalopathy is a cognitive impairment that affects the patient's quality of life and socioeconomic condition. Evidence shows that this state of persistent cognitive impairment is accompanied not only by systemic inflammation and high ammonia levels, but also by a reduction in albumin levels and its ability to bind to metabolites that precipitate HS in patients with advanced cirrhosis. In the study conducted by FAGN et al., 2023, this hypothesis was proven and it was shown that intravenous albumin is associated with improvement in cognitive dysfunction in individuals with cirrhosis, improving levels of inflammatory markers and endothelial dysfunction when compared to the placebo group. However, it is noteworthy that there was no change in liver disease severity or venous ammonia levels between groups. Such a study demonstrates that albumin therapy improves cognitive performance that persists for up to one week after albumin discontinuation. However, larger studies are needed to validate these findings, since only 2 other studies on the use of albumin have

been conducted, but none of them evaluated the results on the cognitive impairment of patients. (FAGN et al., 2023)

Following the line of reasoning that relates HS to an intestinal dysbiosis, the study by BAJAJ et al., 2019 evaluates the safety of fecal microbiota transplantation (FMT) through oral capsules. FMT has been shown to be safe, well-tolerated, and associated with a favorable change in serum lipopolysaccharide-binding protein (LBP) levels, as well as improving duodenal mucosal barriers and mucosa. However, this study maintained the administration of Rifaximin in patients, raising questions about the results found, since the antimicrobial has similar results already proven. In this sense, further studies are needed to prove the efficacy and corroborate the results found.

Also considering the intestinal dysbiosis identified in patients with cirrhosis, the study conducted by VIDOT et al., 2019 sought to investigate the effects of the administration of synbiotics and/or BCAAs in the treatment of HS. It was considered that the proposed supplementation would promote an increase in the growth and diversity of beneficial bacteria, resulting in improved brain and cognitive function. The results showed no adverse effects of the use of synbiotics and BCAAs, alone or in combination, and demonstrated positive results in the treatment of synbiotics together with BCAAs, suggesting that the combined use of the two compounds could be an effective additional treatment in individuals with HS, thus demonstrating the need and importance of further research in this regard.

Current protocols for the treatment of HS in acute-on-chronic liver failure consist of addressing precipitating factors, correcting electrolytes, treating sepsis and gut dysbiosis, and ammonia-focused therapy such as the use of lactulose and antibiotics. Considering that early bowel evacuation and excretion of ammonia through feces are crucial for the treatment of HS, the possibility of PEG being a better alternative to Lactulose has been discussed. An early bowel purge using PEG3350 has been shown to achieve earlier, longer-lasting, and safer resolution when compared to Lactulose alone. These results demonstrate advantages such as reduced hospital stay and faster recovery with PEG. Despite the reported clinical improvement, ammonia levels did not show significant changes, suggesting that PEG acted in ways other than ammonia reduction. Even if the study demonstrated improved survival and early resolution, the results may be questioned because they were not placebo-controlled and because there was no blinding in the study. In addition, the use of PEG occurred alongside the use of Lactulose, thus raising doubts about the true benefits of PEG. (AHMED et al., 2020)

Another clinical trial that followed this same line of reasoning sought to evaluate the safety and efficacy of polyethylene glycol versus Lactulose, thus investigating the gap observed in the

study by AHMED et al., 2020. The results of this study showed that patients with cirrhosis who received PEG as initial therapy for hepatic encephalopathy showed faster clinical improvement than patients who received Lactulose, favoring the individuals to return to normal life more quickly. PEG was better tolerated and had no serious adverse effects. The study conducted by Shehata et al., 2018 corroborated the results found by AHMED et al., 2020 that PEG would be a good alternative to Lactulose and addressed the questions left by such an assay. Therefore, further research addressing this hypothesis would be beneficial and could cause changes in the currently approved HS treatment.

Although studies have demonstrated a complex and multifactorial etiology for HS, the increase in ammonia levels is considered the key to the pathophysiology of the disease. Ornithine phenylacetate is an ammonia collector capable of reducing ammonia levels independently of intestinal action in patients with cirrhosis. Considering this information, a study conducted by RAHIMI et al., 2021 sought to analyze the efficacy of the drug in the treatment of hepatic encephalopathy. The results showed that there was no difference in the mean time of improvement between the group that received the drug and the placebo group. It was also demonstrated that the safety profile of the drug supports further studies to be carried out in the future in order to corroborate the results found. Another study conducted by SAFADI et al., 2022 sought to characterize the pharmacokinetics and pharmacodynamics of Ornithine Phenylacetate (OP), considering the plasma level of ammonia as the primary pharmacodynamic variable. OP was significantly superior to placebo in terms of reducing plasma ammonia levels and the time required for these levels to normalize, and is directly related to the dose used (dose-dependent). The studies also demonstrated the correlation between ammonia values and clinical response, in line with the results found in the study conducted by RAHIMI et al., 2021. In this sense, it is possible to question the results found in the study conducted by SAFADI et al., 2022, since, in addition to presenting discrepant results from the other, a reduction in ammonia levels was also observed in the placebo group. Considering that both the placebo group and the test group received standard therapy during their hospital stay, and that the placebo group also showed improvement, questions arise about the extent to which ornithine phenylacetate was actually beneficial. In addition, in the study by SAFADI et al., 2022, the OP dose was not randomized, but calculated based on individual parameters of each patient. Thus, we conclude the need for larger trials to evaluate OP in the treatment of hepatic encephalopathy, since the two studies used in this study reached different conclusions regarding the clinical progression of the disease.

In the various forms of division proposed for hepatic encephalopathy, the disease can be divided into minimal/subclinical, mild or severe according to the clinical manifestations presented. The therapeutic basis currently approved is focused on manifested HS, so there is no treatment directly indicated for the subclinical type. A study conducted by Montagnese et al., 2021 considered that the cognitive problems presented at this stage of the disease could be improved by a drug designed to normalize the function of receptors that inhibit brain function, Golexanolon. This hypothesis can be corroborated by other recent studies that suggest that the cerebral effects of hyperammonemia and other injuries such as neuroinflammation are mediated by neurosteroid-induced allosteric activation of GABA-A inhibitory receptors. The GABA system, the brain's main inhibitory neutrotransmitter system, regulates functions such as learning, memory, wakefulness and sleep. In addition to GABA, endogenous neurosteroids such as alognanolone are strong positive allosteric modulators mediated by the activation of GABA-A receptors and are present in increased amounts in the brains of HS patients. Following this line of reasoning, the study demonstrated benefits of Golexanolonone in the cognitive performance of patients with HS, being generally well tolerated, supporting the hypothesis of the role of neurosteroids in the pathogenesis of disease-related sleepiness. It is necessary that larger studies be carried out to prove these findings.

5 CONCLUSION

Hepatic encephalopathy is one of the most serious complications of liver cirrhosis, presenting as a debilitating condition that affects the patient's quality of life and brings high health costs. Rapid recognition and correct management of hepatic encephalopathy are directly related to the clinical improvement of the individual.

Treatment is based on the elimination of triggers and toxic substances from the intestine. The currently approved therapeutic measures are Lactulose and the use of antibiotics such as Rifaximin and Metronidazole. It is also necessary to provide energy and protein, in addition to being careful with glycemic values and hydroelectrolyte disorders.

As demonstrated throughout this study, several interventions have been suggested and studied for the prevention and treatment of hepatic encephalopathy, such as the use of albumin, fecal transplantation by oral capsules, polyethylene glycol, Ornithine Phenylacetate, synbiotics, BCAAs and Golexanolon. However, more research and studies are needed.

Considering the great impact caused by HS and the high risk of death associated with this disease, further studies in this regard are important to increase therapeutic accuracy and ensure excellent treatment and better quality of life for affected individuals.

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