https://doi.org/10.23873/2074-0506-2021-13-3-235-247

Results of using L-ornitin-L-aspartate in the treatment of hepatic encephalopathy in liver transplantation

S.E. Voskanyan, E.V. Naydenov✉, A.I. Artemev, D.A. Zabezhinskiy, K.K. Gubarev, V.S. Rudakov, M.V. Shabalin, D.S. Svetlakova, A.P. Maltseva, Yu.V. Voskanyan, A.G. Naydenova, M. Muktarzhan, Z. Sadykhov

State Research Center – Burnasyan Federal Medical Biophysical Center of Federal Medical Biological Agency, 23 Marshal Novikov Str., Moscow 123098 Russia

✉Corresponding author: Evgeniy V. Naydenov, Cand. Sci. (Med.), Surgeon of Surgical Department No. 2, Senior Researcher of the Laboratory for New Surgical Technologies of the Center for Surgery and Transplantation, State Research Center – Burnasyan Federal Medical Biophysical Center of Federal Medical Biological Agency, e.v.naydenov@mail.ru

Abstract

The aim *was to study the results of using various treatment regimens for hepatic encephalopathy for patients with liver cirrhosis before and after liver transplantation and the effect on the incidence and severity of hepatic encephalopathy in the perioperative period, and on the posttransplantation course.*

Material and methods. *Fifty four patients with cirrhosis of various etiologies and the presence of significant hepatic encephalopathy undergoing living donor liver transplantation were included in the study. In the comparison group, patients took lactulose and rifaximin. In the main group, patients took lactulose and rifaximin in combination with L-*

ornithine-L-aspartate in the preoperative period, and L-ornithine-L-aspartate after liver transplantation for 5 days.

Results. *The use of L-ornithine-L-aspartate in the complex therapy of hepatic encephalopathy led to significantly reduced time of performing the Number Connection Test, the improvement of cognitive functions in patients by the Montreal Cognitive Assessment, a decreased incidence of stage II-III hepatic encephalopathy and an increased incidence of stage 0-I hepatic encephalopathy in the preoperative period. In the postoperative period, patients of the main group showed a rapid decrease in the severe stages of hepatic encephalopathy (stage II-III) towards less severe forms (stage 0-I) on the* 3^{rd}, 5^{th}, *and* 7^{th} *days after liver transplantation, and also a faster recovery of cognitive functions, an earlier adequate recovery of consciousness, muscle tone, an earlier possibility of extubation, a shorter length of stay in the intensive care unit, and a decreased postoperative hospital length of stay relatively to the patients of the comparison group.*

Conclusion. *The use of L-ornithine-L-aspartate in the combination therapy for hepatic encephalopathy in the peritransplantation period leads to a significant decrease of the incidence and severity of hepatic encephalopathy, accelerates rehabilitation of patients, reduces postoperative hospital length of stay.*

Keywords: hepatic encephalopathy, liver cirrhosis, liver transplantation, L-ornithine-L-aspartate

Conflict of interests Authors declare no conflict of interest

Financing The study was performed without external funding

For citation: Voskanyan SE, Naydenov EV, Artemev AI, Zabezhinskiy DA, Gubarev KK, Rudakov VS, et al. Results of using L-ornitin-L-aspartate in the treatment of hepatic encephalopathy in liver transplantation. *Transplantologiya. The Russian Journal of Transplantation.* 2021;13(3):235–247. (In Russ.). https://doi.org/10.23873/2074-0506-2021-13-3-235-247

GIT, gastrointestinal tract

HE, hepatic encephalopathy

INR, International Normalized Ratio

LC, liver cirrhosis

LOLA, L-Ornithine-L-Aspartate

LT, liver transplantation

MoCA, Montreal Cognitive Assessment

Introduction

Hepatic encephalopathy (HE) is defined as a neuropsychiatric syndrome that develops against the backdrop of severe diffuse liver lesions and is manifested by behavioral and consciousness disorders, and neuromuscular impairments caused by metabolic disorders, which could be formed due to an acute liver cellular failure, diffuse chronic liver diseases, impaired liver detoxification function, and portal blood shunting [1-7].

HE most commonly occurs as a result of hepatocellular failure (considered as the leading cause), as well as against the background of forced diuresis, gastrointestinal bleeding, paracentesis, surgical interventions, alcoholic excesses, infectious diseases (including spontaneous bacterial peritonitis), increased protein intake, inflammatory diseases of the colon, constipation, portosystemic shunting, the use of

benzodiazepine derivatives or opiates, hypokalemia, and hypovolemia [1-3, 5].

In current understanding, the basis of HE pathogenesis is attributed to the toxic effect of ammonia on astrocytes as a result of hyperammonemia and impaired permeability of the blood-brain barrier [1, 6-8]. In diffuse liver disease and the development of portosystemic shunting, the main causes of hyperammonemia include an increased absorption of ammonia in the gut, an impaired detoxification of ammonia in the liver, impaired kidney function and alkalosis due to the chronic use of diuretics, a depletion of kidney intravascular volume, and a decreased degree of ammonia binding in hypotrophic skeletal muscles (decrease of glutamine synthetase activity) [1–3, 7].

The HE clinical presentation is diverse, characterized by a wide range of neuropsychic manifestations -- from minimal asymptomatic forms (Stage 0) according to the West Haven Criteria to coma (Stage 4) [1–3, 5, 7–9].

HE treatment still remains an unsolved problem and requires a large amount of medical care for a long time [2, 7]. The main areas of therapeutic measures in HE include identifying and addressing the factors that cause liver damage and provoke the development/growth of HE, reducing the absorption of nitrogenous substances from the gastrointestinal tract (GIT); reducing the severity of portosystemic shunting; decreasing the formation and absorption of ammonia or increasing its elimination, reducing brain abnormalities caused by the liver failure [1, 7, 8]. Taking into account the peculiarities of HE pathogenesis, the therapeutic treatment aimed at reducing the level of the blood serum ammonia (mainly through its inhibition in the gastrointestinal tract) and its removal is most effective in HE [1, 3, 7–10]. For this purpose, lactulose, unabsorbable disaccharide, has been widely

used, which, when administered, undergoes metabolic transformations under the effect of the colon microflora, forming lactic, acetic and formic acids, which is accompanied by a decrease in pH and increase in osmolarity of intraluminal content, resulting in reduced production and absorption of ammonia, in accelerated passage of intestinal contents, minimized impact of colon microflora waste products on the central nervous system [1–3, 5, 7–10].

The use of various oral antibiotics is justified by their effect on microorganisms that produce nitrogenous compounds in the gastrointestinal tract [1, 3, 10]. However, there is no convincing evidence for the efficacy of these drugs, and a large number of possible undesirable effects prevent their use as "first-line" drugs in the treatment of HE [1, 3].

An important role in the treatment of HE belongs to the antibiotic rifaximin-α, which is a semi-synthetic derivative of Rifamycin; it has a wide spectrum of antibacterial activity against a large number of bacteria with a bioavailability of 0.5%, which makes it a very safe drug [1, 3, 5, 7–11].

Recently in clinical practice, L-ornithine-L-aspartate (LOLA) has been actively used for the treatment of HE. LOLA is considered one of the most successful drugs currently used to neutralize ammonia [1, 2, 5, 7-10, 12, 13]. The mechanism of the protective effect of the drug is associated with a decrease in the level of blood ammonia, which occurs in parallel with an increase in the formation of urea, glutamate and glutamine [1, 2, 5, 7, 10, 12, 13]. LOLA has a dual mechanism by integrating both amino acids into the ornithine cycle. LOLA increases protein tolerance and has an anabolic effect, increases the energy potential of cells, increases the lactic acid utilization. The membrane-stabilizing effect determines the antioxidant effect of LOLA, which is especially significant in chronic liver diseases. The use of LOLA has

proven effective not only in reducing hyperammonemia and the severity of this disease, but also in improving the quality of life of patients [3, 9, 12, 13].

The study objective was to investigate the results of various treatment regimens for HE in patients with liver cirrhosis (LC) before and after liver transplantation (LT) and to study their impact on HE incidence and severity in the perioperative period, and on the post-transplant course.

Material and methods

In the period from January 2009 to April 2020, 377 LTs were performed for liver diffuse and focal lesions at the Center for Surgery and Transplantation of the State Research Center – Burnasyan Federal Medical Biophysical Center of Federal Medical Biological Agency (Moscow) [14-16]. This retrospective study included 54 patients with LC of various etiologies and significant HE. The age of the patients was 42 (35-51) years old and ranged from 18 to 64 years. There were 26 men and 28 women. The identified LC was of HCV etiology in 15 patients, of HBV etiology in 24 patients, and of other etiologies (primary biliary LC, LC against the backdrop of primary sclerosing cholangitis, cryptogenic LC, etc.) in 15 patients. All patients underwent an examination and treatment prior to close-related donor right lobe liver transplantation. All patients underwent a comprehensive examination, which included liver function tests; the determination of international normalized ratio (INR), blood albumin, blood creatinine, blood urea, sodium levels; abdominal ultrasound examination, esophagogastroduodenoscopy. The patients with concomitant neurological or psychiatric pathology were not included in the study.

In the preoperative period, all patients received a standard conservative therapy, including diuretic, antibacterial, hepatoprotective therapy [17] and albumin infusion, if necessary.

Patients were allocated into groups with regard to HE treatment methods. Group 1 (the comparison group) included 27 patients who, in addition to the standard therapy, took lactulose at a dose of 20-30 g 2-3 times a day and rifaximin at a dose of 400 mg 3 times a day for 7 days. Group 2 consisted of 27 patients who were treated for HE with lactulose at a dose of 20–30 g 2–3 times a day, rifaximin at a dose of 400 mg 3 times daily in combination with LOLA in a dosage of 10 g 2 times a day intravenously for 7 days in the preoperative period, followed by intravenous LOLA therapy at a dose of 10 g 2 times a day for 5 days in the postoperative period. In clinical, instrumental, and laboratory parameters, the patient groups were comparable (Table 1).

Table 1. Clinical parameters and instrumental test results of the investigated patients

Parameter	Group 1	Group 2	p
Gender (m/f)	13/14	13/14	>0.05
Age, years	47 (36–52)	40 (34–49)	>0.05
Etiology (viral hepatitis C and B/others)	10/11/6	5/13/9	>0.05
Child-Pugh (B/C)	11/16	10/17	>0.05
MELD	20 (16–27)	22 (18–25)	>0.05
Albumin	34.2 (29.4–38.2)	34.5 (29.6–37.8)	>0.05
Blood bilirubin (total)	65.6 (49.8–142.6)	67.7 (56.5–190.6)	>0.05
Blood bilirubin (direct)	19.2 (11.9–54.3)	23.5 (12–155.9)	>0.05
Alanine aminotransferase	38.1 (23–78.4)	54.9 (27.5–83.1)	>0.05
Aspartate aminotransferase	70.8 (38.1–112.6)	74.7 (39.1–127.3)	>0.05
Blood creatinine	62 (53.3–77.1)	58.7 (51.9–72)	>0.05
Blood urea	4.3 (3.2–5.8)	3.8 (3.3–5.3)	>0.05
Serum sodium	138 (134.4–141)	139 (135–142)	>0.05
INR	1.53 (1.34–1.74)	1.38 (1.33–1.71)	>0.05
Number Connection Test	113 (91–134)	126 (93–132)	>0,05

Diagnosis of HE was made based on a detailed conversation with the patient, as well as his immediate family members, medical history, clinical manifestations of HE, and the results of the Number Connection Test before and after the course of therapy.

The main symptoms that characterize HE in patients of the compared groups are presented in Table 2.

Table 2. The main symptoms of hepatic encephalopathy before starting the therapy

Parameter	Patient groups		p
	Group 1	Group 2	
Shortened attention span	100%	100%	>0.05
Neuromuscular disorders (changes in handwriting, tremors, etc.)	85.2%	88.9%	>0.05
Memory decline	70.4%	74.1%	>0.05
Sleep disturbance	77.8%	74.1%	>0.05

The HE was graded according to the West Haven Criteria 1994, in the preoperative period before and after HE treatment, as well as at 3, 5, and 7 days after surgery, [2, 4, 18].

Among the patients in group 1, 3 patients (11.1%) had Stage 1 HE, 11 patients (40.7%) had Stage 2 HE, and 13 patients (48.1%) had Stage 3 HE. In the group 2 of patients, 2 patients (7.4%) had Stage 1 HE, 10 patients had Stage 2 HE, and 15 patients (55.6%) had Stage 3 HE (Table 3).

Table 3. Distribution of patients by stages of hepatic encephalopathy (according to West-Haven criteria)

Stage of hepatic encephalopathy	Patient groups		p
	Group 1	Group 2	
Stage 1	11.1%	7.4%	>0.05
Stage 2	40.7%	40.7%	>0.05
Stage 3	48.1%	51.9%	>0.05

In addition, patients were evaluated for cognitive functions according to the Montreal Cognitive Assessment (MoCA) [19] in the preoperative period before and after treatment for HE, as well as 5 days after LT. The results of the assessment of cognitive functions in groups of patients before the treatment for HE are presented in Table 4.

Table 4. Distribution of patients after the assessment of cognitive functions before the treatment of hepatic encephalopathy (according to the Montreal Cognitive Assessment)

MoCA (scores)	Patient groups		p
	Group 1	Group 2	
< 26	88.9%	96.3%	>0.05
≥ 26	11.1%	3.7%	>0.05

In the postoperative period, we studied the time of an adequate recovery of consciousness and transfer of patients to spontaneous breathing (extubation time), patient's length of stay in the intensive care unit and the number of postoperative bed-days, meantime the patients with surgically complicated postoperative course were not included in the study.

Quantitative data are presented as "median (interquartile range)". The statistical significance between dependent groups was assessed using the Wilcoxon test, and that between independent groups was assessed using the Mann–Whitney U-test and χ^2 test with the level of statistical significance $p<0.05$. Statistical processing of the study results was performed using “Statistica 10.0” software package (StatSoft inc., USA) [20].

Results

After using LOLA in combination with lactulose and rifaximin, all patients in Group 2 noted an improvement in their general condition, improved weakness, attention, memory, and sleep, and a decrease severity of neuromuscular disorders (Table 5).

Table 5. The main symptoms of hepatic encephalopathy before and after starting the therapy in the preoperative period

Parameter	Patient groups			
	Group 1		Group 2	
	Before	After	Before	After
Shortened attention span	100%	88.8%	100%	66.7%*^
Neuromuscular disorders (changes in handwriting, tremors, etc.)	85.2%	70.4%	88.9%	40.7%*^
Memory decline	70.4%	59.3%	70.4%	29.6*^
Sleep disturbance	55.6%	48.1%	63.0%	22.2%*^

Note: * - $p < 0.05$ (Wilcoxon test) compared to the previous value;

^ - $p < 0.05$ (Mann-Whitney U-test) in relation to the results in the comparison group.

Seven days after the start of the conservative therapy course, patients in group 1 showed a statistically significant decrease in the time to pass the Number Connection Test compared to that before the start of the treatment, and it made 98 seconds (75-111). However, when LOLA was added to the therapy (patient group 2), the test completion time was significantly reduced and made 49 seconds (40-85) and was statistically significantly lower compared both to the value before the therapy start and to the results obtained in the comparison group ($p<0.05$) (See Figure).

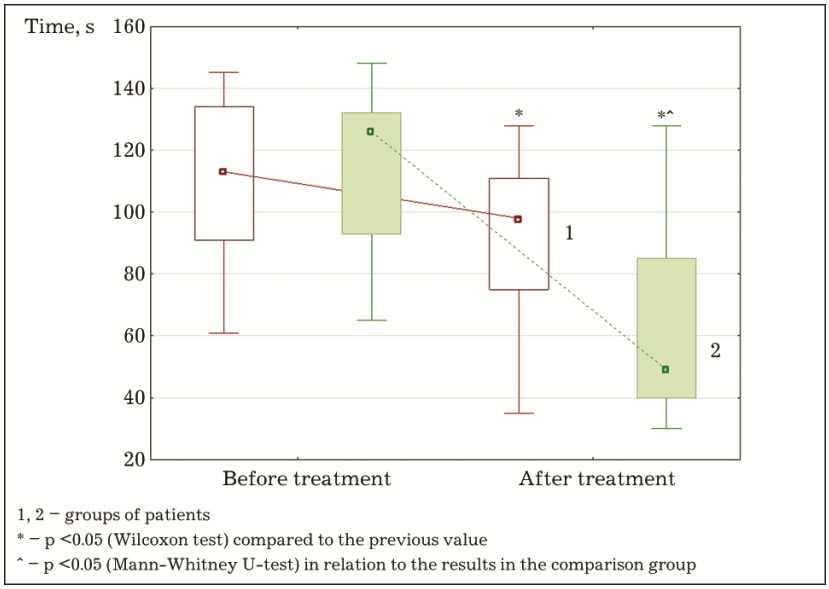

Figure. The effect of different treatment regimens for hepatic encephalopathy on the time of the Number Connection Test

The LOLA use in the complex therapy for HE (patients of Group 2) led to a statistically significant decrease of Grade 2-3 HE and an increase in the frequency of Grade 0–1 HE in relation both to the values before the start of the therapy and to the corresponding values in the comparison group (Table 6).

Table 6. The effect of using different treatment regimens for hepatic encephalopathy in the preoperative period (according to West-Haven criteria)

Stage of hepatic encephalopathy	Patient groups			
	Group 1		Group 2	
	Before	After	Before	After
Stage 0	0	3.7%	0	25.9%*^
Stage 1	11.1%	14.8%	7.4%	44.4%*^
Stage 2	40.7%	40.7%	40.7%	14.8%*^
Stage 3	48.1%	40.7%	51.9%	14.8%*^

Note: * - p <0.05 (Wilcoxon test) compared to the previous value;

^ - p <0.05 (Mann-Whitney U-test) related to the results in the comparison group.

When assessing cognitive functions using MoCA at 7 days after the treatment, patients in the second group showed a statistically significant

improvement in cognitive functions compared to the values before the therapy start, and to those in the comparison group (Table 7).

Table 7. The effect of various treatment regimens for hepatic encephalopathy on the cognitive functions of patients in the preoperative period (according to the Montreal Cognitive Assessment)

MoCA (scores)	Patient groups			
	Group 1		Group 2	
	Before	After	Before	After
< 26	88.9%	77.8%	96.3%	51.9%*
≥ 26	11.1%	22.2%	3.7%	48.1%*^

Note: * - p <0.05 (Wilcoxon test) compared to the previous value;

^ - p <0.05 (Mann-Whitney U-test) related to the results in the comparison group.

The LOLA use in the postoperative period in patients who had been treated with LOLA in combination with lactulose and rifaximin at the preoperative stage led to a more rapid decline in HE severity grades (Stage 2-3) to more mild forms (Stage 0–1) at post-LT days 3, 5, and 7 relative to those in the comparison group (Table 8).

Table 8. Distribution of patients by stages of hepatic encephalopathy after liver transplantation (according to West-Haven criteria)

Patient groups / Day post surgery		Stage of hepatic encephalopathy			
		Stage 0	Stage 1	Stage 2	Stage 3
Group 1	Before surgery	3.7%	14.8%	40.7%	40.7%
	Day 3	14.8%	25.9%	33.3%	25.9%
	Day 5	18.5%	40.7%	22.2%	18.5%
	Day 7	51.8%	29.6%	14.8%	3.7%
Group 2	Before surgery	25.9%^	44.4%^	14.8%^	14.8%^
	Day 3	48.1%^	37.0%	11.1%^	3.7%^
	Day 5	85.2%^	14.8%^	0^	0^
	Day 7	92.6%^	7.4%^	0^	0

Note: ^ - p <0.05 (Mann-Whitney U-test) related to the results in the comparison group

The LOLA use in the combined treatment for HE resulted in a more rapid recovery of cognitive functions in this group of patients compared to patients who did not receive LOLA (Table 9).

Table 9. The effect of various treatment regimens for hepatic encephalopathy on the cognitive functions of patients before liver transplantation and on Day 5 of the postoperative period (according to the Montreal Cognitive Assessment)

MoCA (scores)	Patient groups			
	Group 1		Group 2	
	Before	After	Before	After
< 26	77.8%	25.9%*	51.9%	0*^
≥ 26	22.2%	74.1%*	48.1%	100.0%*^

Note: * - p <0.05 (Wilcoxon test) compared to the previous value;

^ - p <0.05 (Mann-Whitney U-test) related to the results in the comparison group.

In addition, patients of group 2 showed a more rapid recovery in the postoperative period, which was characterized by a statistically significant ($p<0.05$) decrease in the postoperative hospital length of stay (20 days (*17-22*) in the main group of patients versus 25 days (*18-30*) in the comparison group).

There were no side effects related to the prescribed therapy in neither group of patients. There was no hospital mortality.

Discussion of results

Hepatic encephalopathy is a severe complication of diffuse chronic liver diseases, most often it develops in patients with LC and is noted in 30-80% of cases, and a much higher percentage of these patients may have a minimal or latent stage of encephalopathy [3]. HE significantly reduces the quality of life of both the patients and their relatives due to the need for constant care and monitoring of their condition; and the

prevalence of HE correlates with the LC severity and is an important indicator of decompensation [2, 4, 6]. In most patients with LC, the mortality rate after the HE onset, makes 50% within a year, and about 80% within 5 years as a result of an increasing hepatocellular insufficiency [1].

As indicated in the EASL/AASLD guidelines for the treatment and prevention of HE, the combination of rifaximin-α with lactulose is effective for preventing the severe HE recurrence [1, 2, 9].

Recently LOLA has actively been used in the clinical practice of the treatment for HE. LOLA contains two important active ingredients: ornithine (the substrate of the uric acid cycle; its functional potential in LC is significantly limited) and aspartate (that converts to glutamate in a transamination reactions) activating the ornithine cycle of ammonia detoxification; LOLA is considered one of the most successful drugs used currently to detoxify ammonia [1, 2, 5, 7–10, 12, 13].

Our study showed the positive effect of using LOLA in combination with the rifaximin and lactulose in the treatment of HE on its incidence and severity; the patients showed the improvement in general condition, the number of patients with shortened attention span, neuromuscular disorders, memory decline and sleep disturbance decreased, the number of patients without disturbances of cognitive functions, according to MoCA, increased; the positive Number Connection Test results were seen in most patients compared to the patients who were treated for HE with rifaximin and lactulose only.

LT is the only way to treat end-stage diffuse liver diseases, regardless of their etiology. Most of these patients have HE of varying severity, which significantly affects the surgery results and the postoperative course [21]. Up to 50% of patients who have undergone LT for chronic liver disease suffer from HE after surgery, and of these, 35% to 45% of

patients had a history of HE episodes [22, 23], which is currently considered a risk factor for HE development in the first weeks after LT [23]. In the first weeks after LT, 30% of patients develop disorientation, confusion, blurred consciousness, hallucinations, or convulsions [23]. At the same time, patients without HE before LT showed a significant decrease in the frequency of manifested cognitive impairments during the first year after surgery [22]. LT takes away the underlying chronic liver disease that causes HE by definition, and thus effectively eliminates hyperammonemia, the suspected main pathogenic factor of HE. Until recently, HE has been considered to be completely reversible; however, some degree of cognitive impairments may persist in patients after LT, as well as in the patients who did not undergo transplantation, after HE resolution [21, 24], and the sequelae of neurological complications are the consequence of HE in the preoperative period [25]. The presence of HE in patients with LC leads to a worse prognosis after LT [24]. Analyzing the literature data, we can conclude that the treatment of HE in the peritransplantation period is a necessary measure.

Our study has shown that using LOLA in combination with rifaximin and lactulose before LT with further isolated LOLA use in the postoperative period significantly reduced the number of patients with severe forms of HE, increased the number of patients with mild HE, led to a more rapid recovery of cognitive functions in patients with preoperative HE and also reduced the patients' length of stay in the intensive care unit and postoperative patients' hospital length of stay compared to those in the patients who were preoperatively treated for HE with rifaximin and lactulose only.

Currently, the principal method of HE treatment is the conservative therapy, which includes the combined use of lactulose, alpha-rifaximin, and LOLA [3].

Our experience of using L-ornithine-L-aspartate in combination with rifaximin and lactulose in the treatment of severe hepatic encephalopathy in patients with liver cirrhosis shows its good tolerability, safety and efficacy; based on this, the use of L-ornithine-L-aspartate may be recommended for the treatment of hepatic encephalopathy, including the patients who are planned for liver transplantation.

Conclusions

1. The use of L-ornithine-L-aspartate in the combined treatment of hepatic encephalopathy in patients with liver cirrhosis improves their general condition, reduces weakness, improves attention, memory, sleep, reduces neuromuscular disorders, reduces the time to pass the Number Connection Test, and accelerates the recovery of cognitive functions (according to the Montreal Cognitive Assessment) in the peritransplantation period.

2. The use of L-ornithine-L-aspartate in combination with lactulose and rifaximin before and after liver transplantation leads to a more rapid decrease in the severity of hepatic encephalopathy and a marked decrease (by 20%) in the duration of postoperative recovery of patients.

References

1. Pavlov ChS, Damulin IV, Ivashkin VT. Hepatic encephalopathy: pathogenesis, clinical features, diagnosis, therapy. *Russian Journal of Gastroenterology, Hepatology, Coloproctology.* 2016;26(1):44–53. (In Russ.).

2. Poluhina AV, Hajmenova TYu, Vinnickaya EV. Hepatic encephalopathy: a problem of pharmacotherapy. *Meditsinskiy sovet.* 2018;(3):43-48. (In Russ.).

3. Plotnikova EYu, Baranova EN, Maksimov SA. The relationship of hepatic encephalopathy with zinc in liver diseases, diagnosis and treatment. *Gastroenterology.* 2017;(4):33–40. (In Russ.).

4. Weissenborn K. Hepatic encephalopathy: definition, clinical grading and diagnostic. *Drugs.* 2019;79(Suppl 1):5–9. PMID: 30706420 https://doi.org/10.1007/s40265-018-1018-z

5. Elwir S, Rahimi RS. Hepatic encephalopathy: an update on the pathophysiology and therapeutic options. *J Clin Transl Hepatol.* 2017;5(2):142–151. PMID: 28660152 https://doi.org/10.14218/JCTH.2016.00069

6. Patidar KR, Bajaj JS. Covert and overt hepatic encephalopathy: diagnosis and management. *Clin Gastroenterol Hepatol.* 2015;13(12):2048–2061. PMID: 26164219 https://doi.org/10.1016/j.cgh.2015.06.039

7. Suraweera D, Sundaram V, Saab S. Evaluation and management of hepatic encephalopathy: current status and future directions. *Gut Liver.* 2016;10(4):509–519. PMID: 27377741 https://doi.org/10.5009/gnl15419

8. Nikonov EL, Aksenov VA. Hepatic encephalopathy. *Dokazatel'naya gastroenterologiya.* 2017;(4):25–31. (In Russ.).

9. Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American Association for the study of liver diseases and the European Association for the study of the liver. *Hepato-logy.* 2014;60(2):715–735. PMID: 25042402 https://doi.org/10.1002/hep.27210

10. Leise MD, Poterucha JJ, Kamath PS, Kim WR. Management of hepatic encephalopathy in the hospital. *Mayo Clin Proc.* 2014;89(2):241–253. PMID: 24411831 https://doi.org/10.1016/j.mayocp.2013.11.009

11. Salehi S, Tranah TH, Lim S, Heaton N, Heneghan M, Aluvihare V, et al. Rifaximin reduces the incidence of spontaneous

bacterial peritonitis, variceal bleeding and all-cause admissions in patients on the liver transplant waiting list. *Aliment Pharmacol Ther.* 2019;50(4):435–441. PMID: 31169941 https://doi.org/10.1111/apt.15326

12. Butterworth RF, McPhall MJW. L-Ornithine L-Aspartate (LOLA) for hepatic encephalopathy in cirrhosis: results of randomized controlled trials and meta-analyses. *Drugs.* 2019;79(Suppl 1):31–37. PMID: 30706425 https://doi.org/10.1007/s40265-018-1024-1

13. Butterworth RF, Kircheis G, Hilger N, McPhail MJW. Efficacy of L-Ornithine L-Aspartate for the treatment of hepa-tic encephalopathy and hyperammonemia in cirrhosis: systematic review and meta-analysis of randomized controlled trials. *J Clin Exp Hepatol.* 2018;8(3):301–313. PMID: 30302048 https://doi.org/10.1016/j.jceh.2018.05.004

14. Artemiev AI, Naidenov EV, Zabezhinsky DA, Gubarev KK, Kolyshev IYu, Rudakov VS, et al. Liver transplantation for unresectable echinococcus alveolaris. *Sovremennye tekhnologii v meditsine.* 2017;9(1):123–128. (In Russ.).

15. Voskanyan SE, Artemyev AI, Sushkov AI, Kolyshev IY, Rudakov VS, Shabalin MV, et al. Vascular reconstruction and outcomes of 220 adult-to-adult right lobe living donor liver transplantations. *Almanac of Clinical Medicine.* 2018;46(6):598–608. (In Russ.).

16. Voskanyan SE, Artemiev AI, Naidenov EV, Zabezhinsky DA, Chuchuev ES, Rudakov VS, et al. Transplant technologies for surgical treatment of the locally advanced hepatic alveolar echinococcosis with invasion of the main vessels. *Annaly khirurgicheskoy gepatologii.* 2016;21(2):25–31. (In Russ.).

17. Voskanyan SE, Naidenov EV, Artemiev AI, Zabezhinsky DA, Rudakov VS, Zhurbin AS, et al. Comparative results of use of the hepatoprotective drugs in the prevention of the liver failure at extensive

liver resections. *Hirurgija. Zhurnal im. N.I. Pirogova*. 2016;(9):71–75. (In Russ.).

18. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy – definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. *Hepatology.* 2002;35(3):716–721. PMID: 11870389 https://doi.org/10.1053/jhep.2002.31250

19. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V. The montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53(4):695–699. PMID: 15817019 https://doi.org/10.1111/j.1532-5415.2005.53221.x

20. Rebrova OYu. Once again of the qua-lity of statistical analysys in medical publications: current status of the problem, recommendations, peer reviewing. *Medical technologies. Assessment and choice*. 2014;15(1):8–10. (In Russ.).

21. Kornerup LS, Pflugrad H, Weissenborn K, Vilstrup H, Dam G. Cognitive impairment after liver transplantation: residual hepatic encephalopathy or posttransplant encephalopathy? *Hepat Med*. 2019;11:41–46. PMID: 31040728 https://doi.org/10.2147/HMER.S144667

22. Hopp A-E, Dirks M, Petrusch C, Goldbecker A, Tryc AB, Barg-Hock H, et al. Hepatic encephalopathy is reversible in the long term after liver transplantation. *Liver Transpl.* 2019;25(11):1661–1672. PMID: 31437344 https://doi.org/10.1002/lt.25626

23. Pflugrad H, Tryc AB, Goldbecker A, Barg-Hock H, Strassburg C, Klempnauer J, et al. Cerebral metabolite alterations in patients with posttransplant encephalopathy after liver transplantation. *PLoS ONE.*

2019;14(8):e0221626. PMID: 31442276 https://doi.org/10.1371/journal.pone.0221626

24. Lucidi C, Corradini SG, Abraldes JG, Merli M, Tandon P, Ferri F, et al. Hepatic encephalopathy expands the predic-tivity of model for end-stage liver disease in liver transplant setting: evidence by means of 2 independent cohorts. *Liver Transpl.* 2016;22(10):1333–1342. PMID: 27434824 https://doi.org/10.1002/lt.24517

25. Weiss N, Thabut D. Neurological complications occurring after liver transplantation: role of risk factors, hepatic encephalopathy, and acute (on chronic) brain injury. *Liver Transpl.* 2019;25(3):469–487. PMID: 30697911 https://doi.org/10.1002/lt.25420

Information about the authors

Sergey E. Voskanyan, Corresponding Member of the Russian Academy of Sciences, Prof., Dr. Sci. (Med.), Deputy Chief Doctor for Surgical Care, Head of the Center for Surgery and Transplantation, State Research Center – Burnasyan Federal Medical Biophysical Center of Federal Medical Biological Agency; Head of the Department of Surgery with courses in oncosurgery, endoscopy, surgical pathology, clinical transplantation and organ donation, Biomedical University of Innovation and Continuing Education, State Research Center – Burnasyan Federal Medical Biophysical Center of Federal Medical Biological Agency, https://orcid.org/0000-0001-5691-5398

25%, development of the study design, obtaining data for analysis, analysis of the data obtained, approval of the article final version, responsibility for the integrity of all parts of the article

Evgeniy V. Naydenov, Cand. Sci. (Med.), Surgeon of the Surgical Department No. 2, Senior Researcher of the Laboratory for New Surgical Technologies of the Center for Surgery and Transplantation, State Research

Center – Burnasyan Federal Medical Biophysical Center of Federal Medical Biological Agency, https://orcid.org/0000-0002-9753-4345

20%, development of the study design, obtaining data for analysis, analysis of the data obtained, statistical processing of data, writing the text of the manuscript, review of publications on the topic of the article, responsibility for the integrity of all parts of the article

Alexey I. Artemev, Cand. Sci. (Med.), Head of Surgical Department No. 2 of the Center for Surgery and Transplantation, State Research Center – Burnasyan Federal Medical Biophysical Center of Federal Medical Biological Agency, https://orcid.org/0000-0002-1784-5945

5%, obtaining the study material, obtaining data for analysis

Dmitriy A. Zabezhinskiy, Cand. Sci. (Med.), Surgeon of the Surgical Department No. 2 of the Center for Surgery and Transplantation, State Research Center – Burnasyan Federal Medical Biophysical Center of Federal Medical Biological Agency, https://orcid.org/0000-0002-5724-6998

5%, obtaining the study material, obtaining data for analysis

Konstantin K. Gubarev, Cand. Sci. (Med.), Head of the Surgical Department for the for the Coordination of Donation of Organs and (or) Human Tissues of, State Research Center – Burnasyan Federal Medical Biophysical Center of Federal Medical Biological Agency, https://orcid.org/0000-0001-9006-163X

5%, obtaining the study material, obtaining data for analysis

Vladimir S. Rudakov, Cand. Sci. (Med.), Surgeon of the Surgical Department for the Coordination of Donation of Organs and (or) Human Tissues of the Center for Surgery and Transplantation, State Research Center – Burnasyan Federal Medical Biophysical Center of Federal Medical Biological Agency, https://orcid.org/0000-0002-3171-6621

5%, obtaining the study material, obtaining data for analysis

Maksim V. Shabalin, Cand. Sci. (Med.), Surgeon of the Surgical Department No. 1 of the Center for New Surgical Technologies, State Research Center – Burnasyan Federal Medical Biophysical Center of Federal Medical Biological Agency, https://orcid.org/0000-0002-4527-0448

5%, obtaining the study material, obtaining data for analysis

Darya S. Svetlakova, Surgeon of the Surgical Department for the Coordination of Donation of Organs and (or) Human Tissues of the Center for Surgery and Transplantation, State Research Center – Burnasyan Federal Medical Biophysical Center of Federal Medical Biological Agency, https://orcid.org/0000-0002-2274-6204

5%, obtaining the study material, obtaining data for analysis

Anna P. Maltseva, Surgeon of the Surgical Department No. 1 of the Center for New Surgical Technologies, State Research Center – Burnasyan Federal Medical Biophysical Center of Federal Medical Biological Agency, https://orcid.org/0000-0003-1192-9598

5%, obtaining the study material, obtaining data for analysis

Yuliya V. Voskanyan, Gastroenterologist at the Polyclinic, State Research Center – Burnasyan Federal Medical Biophysical Center of Federal Medical Biological Agency, https://orcid.org/0000-0003-2445-7382

5%, obtaining the study material, obtaining data for analysis

Anna G. Naydenova, Gastroenterologist of the Polyclinic, State Research Center – Burnasyan Federal Medical Biophysical Center of Federal Medical Biological Agency, https://orcid.org/0000-0002-9346-7413

5%, obtaining the study material, obtaining data for analysis

Marlen Muktarzhan, a Postgraduate of the Department of Surgery with Courses in Oncosurgery, Endoscopy, Surgical Pathology, Clinical Transplantology and Organ Donation Biomedical University of Innovation and Continuing Education, State Research Center – Burnasyan

Federal Medical Biophysical Center of Federal Medical Biological Agency, https://orcid.org/ 0000-0003-4967-1588

5%, obtaining the study material, obtaining data for analysis

Zamin Sadykhov, a Postgraduate of the Department of Surgery with Courses in Oncosurgery, Endoscopy, Surgical Pathology, Clinical Transplantology and Organ Donation, Biomedical University of Innovation and Continuing Education, State Research Center – Burnasyan Federal Medical Biophysical Center of Federal Medical Biological Agency, https://orcid.org/0000-0001-9594-7966

5%, obtaining the study material, obtaining data for analysis

The article was received on March 9, 2021;
approved after reviewing April 1, 2021;
accepted for publication June 30, 2021