Original Article

Oral L-ornithine-L-aspartate for Patients with Overt Hepatic Encephalopathy Treated with Lactulose: A Randomized, Double-blinded, Placebo-controlled Trial

Supot Nimanong MD[1], Inchaya Sansak MD[1],
Tawesak Tanwandee MD[1], Phunchai Charatcharoenwitthaya MD[1],
Watcharasak Chotiyaputta MD[1], Kanokwan Boonyapisit MD[2], Siwaporn Chainuvati MD[1]

[1] Division of Gastroenterology, Department of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand
[2] Division of Neurology, Department of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand

Objective: Lactulose is widely used for treating patients with hepatic encephalopathy [HE] despite of no strong evidence of its effectiveness. L-ornithine-L-aspartate [LOLA] can lower serum ammonia level and improve mental state in patients with mild HE. We evaluated the add-on benefit of oral LOLA in patients with grade II-III HE those treated with optimal dose of lactulose.

Materials and Methods: In a randomized, double-blinded, placebo-controlled trial, cirrhotic patients with grade II and III HE according to West-Haven criteria those treated with lactulose were stratified randomized by serum creatinine level to receive LOLA (3 grams thrice daily) or placebo for 7 days. The primary outcome was the improvement of mental status, and secondary outcomes were the improvement of the number connection test [NCT], plasma ammonia level, asterixis, electroencephalogram [EEG], portal systemic encephalopathy index [PSEI] and safety.

Results: Thirty-five patients with overt HE (grade II 25 patients and grade III 10 patients) were assigned to LOLA group (n = 18) or placebo group (n = 17). The LOLA group tended to have improvement of mental status by 90% compared to 84.6% of placebo group at day 7 (p = 1.0) by per-protocol analysis. Both groups also had similar improvement in mental status at day 4, asterixis, EEG and PSEI. Dose of lactulose and daily bowel movement were comparable in both groups. Treatment of infection which was the main precipitating factor, strongly correlated with better mental state in day 7 (p = 0.025). No serious adverse effect of LOLA was found.

Conclusion: There was no add-on benefit of oral LOLA for cirrhotic patients with overt HE who were treated with an optimal dose of lactulose. The more effective treatment of HE was to correct the precipitating factors especially infection.

Keywords: Ammonia, Cirrhosis, Hepatic encephalopathy, Lactulose, L-ornithine-L-aspartate

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Hepatic encephalopathy [HE] occurs in up to 70% of cirrhotic patients at some times during the course of disease. The prevalence is increased in patients with cirrhosis Child-Pugh class C. The mortality rate of cirrhotic patients with overt HE is up to 30%[1].

Correspondence to:
Nimanong S. Division of Gastroenterology, Department of Medicine, Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.
Phone: +66-2-4197281, **Fax:** +66-2-4115013
E-mail: supot.nim@mahidol.ac.th; supotgi@gmail.com

The optimal treatment of HE is to correct the precipitating factors. Most medications aim to decrease bloodstream ammonia, which plays major role in the pathogenesis of HE[1,2]. Traditionally, non-absorbable antibiotics such as neomycin, kanamycin sulfate and metronidazole are used to reduce colonic bacteria and its ammonia production but there is no strong evidence of their effectiveness and there are numerous adverse effects limiting their long term use[3,4]. Another drug, lactulose, is safe and widely used. It is metabolized by colonic bacterial flora to lactic acid and acetic acid which lower colonic pH and favor the formation of NH_4^+ from

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NH_3, reducing plasma ammonia concentration. However, there is no strong evidence of its effectiveness because 2 previous high-quality trials showed no benefit in improvement of HE despite of optimal dose[5].

L-ornithine-L-aspartate [LOLA] can lower serum ammonia concentration by a different method, providing substrates for urea and glutamine synthesis from ammonia in liver and muscle which are excreted via kidney. Treatment with LOLA is safe and improves mental state and psychomotor performance compared with placebo[6,7]. A small report has shown the benefit of LOLA as compared with lactulose in treatment of patients with mild HE[8]. Therefore, we conducted this randomized, double-blinded, placebo-controlled trial to determine the efficacy and safety of add-on oral LOLA for patients with overt HE, who were treated with an optimal dose of lactulose.

Materials and Methods

Patient population

Adult patients aged 18 to 70 years were eligible for the study if they had cirrhosis with HE grade II or III according to West-Haven criteria. Informed consent was obtained. Subjects were enrolled from Siriraj Hospital, Bangkok, Thailand from February 2008 to February 2009. Subjects were excluded if they had uns table hemodynamics, active gastrointestinal [GI] bleeding, severe sepsis, serum creatinine level more than 3 mg/dL, transjugular intrahepatic portosystemic shunt [TIPS], degenerative brain diseases or major psychiatric illnesses, use of metronidazole, neomycin or LOLA within 2 weeks, use of central nervous system [CNS] depressant or hypnotics, uncontrolled diabetes, pregnancy, lactation, nothing per oral condition or known allergy to LOLA.

Randomization and blinding

The eligible patients were stratified randomized by serum creatinine level (less than 1.50 mg/dL or 1.51 to 3.0 mg/dL) to receive LOLA or placebo for 7 days. A block randomization process with concealed allocation of study medication was followed. The random number sequence was computer generated by a person not associated with the conduct of the study. The study drug and placebo were packed for a period of 7 days according to the code and numbered sequentially from 1 to 40. The boxes were serially allocated when new patients were recruited into

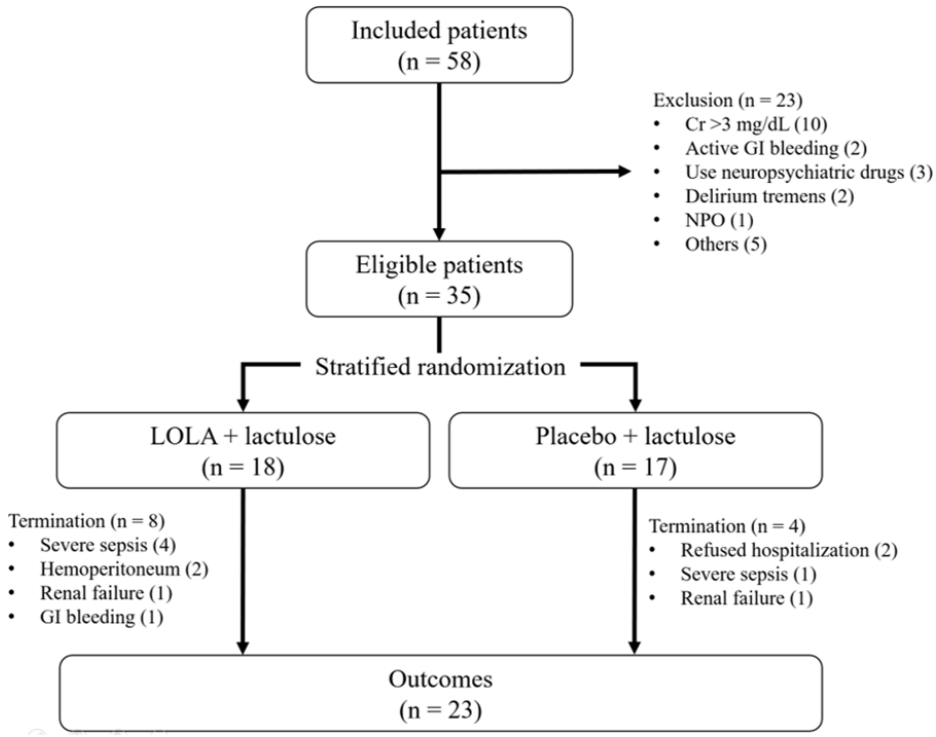

Figure 1. Study protocol

Table 1. Portal-systemic encephalopathy index [PSEI]

	0	1	2	3	4
Mental status	normal disturbance	sleep-wake	lethargy	somnolence	coma
Number connection test (sec)	15 to 30	31 to 50	51 to 80	81 to 120	>120
Serum ammonia (mg/dl)	<60	60 to 80	81 to 100	101 to 120	>120
Asterixis (times/min)	none	1 to 2	3 to 4	5 to 30	Continuous or unable to maintain dorsiflexion
Electroencephalogram (cps)	9 to 12	7 to 8	5 to 6	3 to 4	0 to 2

PSEI = PSE sum/PSE max
= ([mental status x3] + number connection test + ammonia + asterixis + EEG)/28

the study. All of patients were clinically assessed by only one clinician who was not involved in the randomization process and blinded to the type of treatment. Patients were blinded to the identity of the intervention because the placebo was identical to the active drug in packaging, appearance, flavor and schedule of administration.

Study medication

LOLA (Hepa-Merz Granules®, MerzPharma); a 5 gram sachet formulation contained 3 g of LOLA granules. The patient was prescribed 1 sachet, 3 times daily (9 g/d) for 7 days. Both groups of patients received lactulose, a syrup formulation containing 67 g lactulose /100 mL, starting with 30 mL twice daily and adjusted to keep soft stool for 2 to 3 times per day. The empty sachet of study drug/placebo and the amount of lactulose were recorded to assess compliance.

Controlled factors

All patients received low salt (sodium <2 g/d) diet during admission. Bowel movement was controlled by adjusted-dose lactulose to keep soft stool 2 to 3 times per day. Serum potassium was monitored at baseline, on day 4 and day 7 and potassium replacement was given in case of hypokalemia. CNS depressant and hypnotics were avoided during the study. The precipitating factors of HE were corrected.

Enrolled subjects who developed the following events after randomization would be terminated but the data would be analysed by intention-to-treat method. These events included severe sepsis, upper GI hemorrhage, hemoperitoneum, acute renal failure (serum creatinine >3 mg/dL) or receiving CNS depressant and hypnotics.

Outcomes

The primary study endpoint was the improvement in mental status of at least 1 grade according to West-Haven criteria at day 7 after treatment by intention-to-treat analysis. Secondary endpoints included the improvement in number connection test [NCT], serum ammonia level, asterixis at day 4 and day 7, improvement in electroencephalo gram [EEG] and portal-systemic encephalopathy index [PSEI] at the end of the study. The NCT is the time in seconds that a patient required to connect 25 circled numbers. Serum ammonia level were obtained via venous blood samples at fasting state and immediately sent to the laboratory in refrigerated transport. Number of asterixis was recorded for 30 seconds. Frequency (cycle per second) of alpha wave was recorded in EEG. PSEI included mental status, NCT, serum ammonia, asterixis and EEG which is divided by severity for 5 grades (0 to 4) (Table 1) and weighed in accordance with their importance. The total score is divided by the maximal score represents the PSE index.

Statistical analyses

Sample size estimation was based on the following condition. Data from the previous study were used, hypothesizing that the study drug improves mental status for 60% when compared with 10% by lactulose at day 7 of treatment with alpha error of 5% and 90% power. The final number of patients required using the formula ($n = (z_{\alpha/2}/2PQ + z_{\alpha}/(P_1Q_1 + P_2Q_2)/ P_1 - P_2)^2$) was 34 patients.

The statistical evaluation was performed using a SPSS statistical software version 13.0 for Windows. For descriptive data, mean $\pm$ standard deviation was used for quantitative data, number and percentage used

for qualitative data. Unpaired t-test was used to compare mean and Chi-square test was used to compare categorical data. All statistical testing was done at the conventional 2-tailed and α level of 0.05. Per-protocol and intention-to-treat analyses were performed.

Results

A total of 58 cirrhotic patients with HE grade II and III fulfilled the inclusion criteria and 23 patients were excluded. The remaining 35 patients were stratified randomized by serum creatinine level; 24 patients had serum creatinine <1.5 mg/dL and 11 patients had serum creatinine 1.50 to 3.0 mg/dL. Finally, 18 patients were randomized to the LOLA group and 17 patients were randomized to the placebo group. They were followed-up for 7 days but 7 patients were terminated before day 4 (3 patients in LOLA group, 4 patients in placebo group) and 12 patients were terminated before completion of the study (8 patients in LOLA group, 4 patients in placebo group) due to various causes including severe sepsis (4 in LOLA group, 1 in placebo group due to UTI, cellulitis, pneumonia and acute cholangitis), upper GI hemorrhage (1 in LOLA), renal failure (1 in each group), hemoperitoneum (2 in LOLA) and two patients in placebo group refused hospitalization. At the end of the study, 23 patients were included in per-protocol analysis.

Clinical, demographic, and biochemical parameters

There were no difference in gender distribution, body weight, causes of cirrhosis, number of patients who had prior HE or received current treatment with lactulose, co morbidity, severity of cirrhosis, precipitating factors of HE between the two groups at baseline (Table 2). In LOLA group, the patients were older and had less HCC and esophageal varices at baseline. HBV infection and alcohol were the major causes of cirrhosis. Seventy one percent of patients had Child class C cirrhosis and 37.1% of patients also had prior history of HCC, ascites or hepatic encephalopathy. At baseline, 71.4% of patients had HE grade II and 28.6% had HE grade III, mostly precipitated by infection.

Primary outcome

The level of mental status in both groups was comparable at baseline. Sixty percent of patients in LOLA group had improvement of mental status at day 4 compared with 46.2% of patients in placebo group. At the end of the study, 90% of patients in LOLA group had better mental state compared with 84.6% of patients in placebo group respectively, which was not statistically significant (Table 3). Intention to treat analysis also did not demonstrate the difference of the improved mental status between either group. Drug compliance was 99.5% in LOLA group and 99.7% in placebo group.

Secondary outcomes

At baseline, only 5 patients (14.3%) could complete the NCT within 2 minutes (2 in LOLA group and 3 in placebo group, $p = 0.66$). After 7 days of treatment, there was an improvement of the number connection test in LOLA group of only 10% versus 23.1% in placebo group ($p = 0.60$). Serum ammonia levels were not decreased after treatment and the levels were comparable in both groups of patients.

There was marked improvement of asterixis in both groups on day 4 and 7 but the data were comparable ($p = 0.52$ and 0.35, respectively). Frequency of alpha wave of EEG was increased and PSEI was improved at the end of the study in both groups but there were no significant differences (Table 3).

Subgroup analysis

In patients with higher creatinine level (1.6 to 3.0 mg/dL), 3 of 5 (60%) patients in LOLA group had improved mental status compared with none of 4 patients in the placebo group at day 4 but there was no statistical difference ($p = 0.06$).

Lactulose and bowel movement

The patients in both groups received lactulose in differently (55.7$\pm$4.0 mL/day in LOLA group and 58.2$\pm$3.8 mL/day in placebo group). The study group had bowel movements for 3.7$\pm$0.3 times/day comparable with the placebo group (3.4$\pm$0.3 times/day, $p = 0.58$). The percentage of number of days that the patients had bowel movement at least 2 times/day (65.8$\pm$6.8 vs. 69.7$\pm$6.6, $p = 0.69$) and at least 3 times/day (82.3$\pm$4.7 vs. 84.9$\pm$3.9, $p = 0.68$) were also comparable between two groups.

Adverse effects

The most common adverse effect was diarrhea (more than 4 times/day) which occurred 38.8% in LOLA group and 35.3% in placebo group. Most cases of diarrhea were lactulose-induced diarrhea because the symptoms were rapidly resolved after decrease in the dosage of lactulose. Other adverse effects were less common, including bloating, nausea, vomiting and abdominal pain. Hypokalemia was seen in four cases

Table 2. Baseline characteristics of enrolled patients

	Overall (n = 35)	LOLA (n = 18)	Placebo (n = 17)	*p*-value
Age (year)	62.9±1.9	66.9±1.7	58.7±2.1	0.004
Male gender	22 (62.9)	9 (50.0)	13 (76.5)	0.16
Body weight (kg)	63.0±1.9	61.0±1.5	65.1±2.4	0.16
Cause of cirrhosis, n (HBV/HCV/ alcohol/virus+alcohol/others)	7/2/11/3/12	3/1/6/1/7	4/1/5/2/5	0.91
Child-Pugh score: class B/C	10/25	4/14	6/11	0.47
MELD score	21	23	21	0.39
Hepatic encephalopathy: grade 2/3	25/10	11/7	14/3	0.26
Number with creatinine ≤1.5/ 1.51–3.0 mg/dl	24/11	13/5	11/6	0.72
Potassium (mmol/l)	4.1±0.2	4.1±0.2	4.1±0.2	0.83
Total bilirubin (mg/dL)	11.4±3.0	12.1±2.8	10.6±3.3	0.73
Albumin (g/dL)	2.7±0.1	2.7±0.1	2.6±0.1	0.55
Hematocrit (%)	28.9±1.2	29.2±1.5	28.4±0.9	0.68
Platelets (x10^3/ml)	105±11	101±11	111±12	0.54
Serum ammonia (mg/dL)	61.5±7.2	63.2±8.2	59.7±5.9	0.74
Prior cirrhotic complications				
Hepatic encephalopathy	13 (37.1)	6 (33.3)	7 (41.2)	0.73
HCC	13 (37.1)	3 (16.7)	10 (58.8)	0.015
Ascites	20 (57.1)	10 (55.6)	10 (58.8)	1.00
Esophageal varices	13 (37.1)	3 (16.7)	10 (58.8)	0.015
Spontaneous bacterial peritonitis	6 (17.1)	3 (16.7)	3 (17.6)	1.00
Current treatment with lactulose	13 (37.1)	6 (33.3)	7 (41.2)	0.73
Precipitating factors of HE				
Infection	16 (45.7)	9 (50.0)	7 (41.2)	0.74
Upper gastrointestinal hemorrhage	3 (8.6)	0 (0)	3 (17.6)	0.10
Renal failure	5 (14.3)	2 (11.1)	3 (17.6)	0.66
Constipation	6 (17.1)	4 (22.2)	2 (11.8)	0.66
HCC (ruptured / PVT/ post TACE)	5 (14.3)	3 (16.7)	2 (11.8)	1.00
Comorbidity				
Diabetes mellitus	14 (40.0)	5 (27.8)	9 (52.9)	0.17
Hypertension	13 (37.1)	7 (38.9)	6 (35.3)	1.00

HBV = hepatitis B virus; HCV = hepatitis C virus; HCC = hepatocellular carcinoma; HE = hepatic encephalopathy; MELD = model for end-stage liver disease; LOLA = L-ornithine-L-aspartate; PVT = portal vein thrombosis; TACE = transarterial chemoembolization

Data are expressed as number (%) or mean ± SD

due to severe diarrhea. There was no serious adverse effect (Table 4).

Factors determining outcomes

Univariate analysis showed various factors including baseline BUN, creatinine, MELD score, prior SBP, precipitated by infection were associated with unimproved mental state at day 4 and treated infection was associated with poor primary outcome at day 7. Multivariate analysis revealed that only being precipitated by infection was associated with improved mental status at day 4 (OR 0.02, 95% CI 0.01 to 0.75, $p = 0.034$) and treated infection was associated with improved mental status at day 7 (OR 28.1, 95% CI 1.5 to 520.4, $p = 0.025$).

Discussion

The mainstay treatment of HE is to correct precipitating factors such as infection, GI hemorrhage, renal failure, hypokalemia and constipation. Lactulose is safe and widely used especially for patients with constipation although its action is slow and there is no strong evidence of effectiveness, while LOLA which has different mechanism to lower serum ammonia level by promoting urea and glutamine cycle mainly in liver and muscle, may enhance the improvement of mental

Table 3. Outcomes by per-protocol analysis

	Day	LOLA (n = 18)	Placebo (n = 17)	*p*-value
Improvement of HE	4	9/15 (60.0)	6/13 (46.2)	0.70
	7	9/10 (90.0)	11/13 (84.6)	1.00
Improvement of NCT	4	4/15 (26.7)	1/13 (7.7)	0.33
	7	1/10 (10.0)	3/13 (23.1)	0.60
Serum ammonia level (μg/dL)	1	63.2±8.2	59.7±5.9	0.74
	4	59.4±9.9	51.9±6.7	0.56
	7	69.8±11.3	62.2±20.3	0.79
Asterixis (times/30 seconds)	1	16.0±2.4	10.8±1.6	0.09
	4	6.5±2.3	4.4±2.1	0.52
	7	4.5±3.9	1.2±0.8	0.35
EEG (frequency of alpha wave, cps)	1	5.7±0.4	6.4±0.4	0.24
	7	7.0±0.7	7.5±0.2	0.58
PSEI x 100%	1	59.5±8.7	54.3±10.0	0.13
	7	37.8±7.1	30.8±3.2	0.31

HE = hepatic encephalopathy; EEG = electroencephalogram; NCT = number connection test; PSEI = portal-systemic encephalopathy index
Data are expressed as mean ± SD or number (%)

Table 4. Adverse effects

	LOLA (n = 18)	Placebo (n = 17)
Diarrhea (≥5 times/day)	7 (38.8)	6 (35.3)
Bloating	2 (11.1)	2 (11.8)
Nausea	3 (16.7)	0
Vomiting	1 (5.6)	0
Abdominal pain	1 (5.6)	1 (5.9)
Hypokalemia	2 (11.1)	2 (11.8)

Data are presented as number (%)

status in those who received adequate lactulose. However, this randomized, double-blinded, placebo-controlled study has not demonstrated any add-on benefit of oral LOLA for patients with overt HE treated with optimal dose of lactulose.

There are several possible explanations for those unfavorable outcomes. Firstly, the dosage of LOLA may be suboptimal due to the severity of the disease and drug interaction. From previous study[8], oral LOLA was administered for fixed dose (9 g/day) and showed benefit in treatment of patients with HE, but most subjects had mild disease (HE grade I) while in our study, all of patients had overt HE (grade II or III) which were more severe and the prescribed dosage might be inadequate. Moreover, lactulose may reduce the absorption of oral LOLA due to its diarrheal action and decrease its effect. Unfortunately, this hypothesis could not be proved since we could not measure serum level of LOLA to determine the optimal dosage while serum ammonia level, which is the main target of LOLA action, does not correlate with the severity of HE[9,10] and it can be altered by many confounding factors[11].

Secondly, infection is a strong factor which determines outcome in our study. Almost 50% of patients had HE precipitated by infection (most of them were SBP). Multivariate analysis showed that infection was strongly associated with poor outcome at day 4, while treated infection can improve the mental status at the end of the study. These findings support the concept that the most important treatment for HE is to correct the precipitating factors, especially for infection which is its major cause and has a more potent effect than other interventions[12]. Nonetheless, we performed subgroup analysis in the rest of patients who had no infection, but we did not find any difference in outcomes between LOLA and placebo groups. We also found that there was no difference in treatment response between patients with HE grade II or III, or in patients with more advanced liver disease.

Next, there is high drop-out rate in our study. Forty-four percent of patients in LOLA group and 23% of patients in placebo group were terminated before the end of the study, mainly because of worsening HE due to severe sepsis, particularly for LOLA group which resulted in a poor outcome for intention-to-treat

analysis.

Finally, it had small sample size. Since 84.6% of patients in control group had improved mental status at day 7 after receiving lactulose and treating precipitating factors, it required a large number of subjects to demonstrate any significant difference in efficacy of study drug. Subgroup analysis showed that patients with higher creatinine might benefit from LOLA but there is too small sample size to determine.

The outcome measurements for HE are limited, both clinical assessment and psychometric tests[13,14]. Although mental status was assessed by only one clinician in our study, there might be intra-observer variability. Only asterixis and EEG are well correlated with improved mental status, while there is no improvement of NCT and serum ammonia levels despite improved mental status. NCT is not suitable for evaluation of overt HE since 86% of patients could not complete NCT within 2 minutes while serum ammonia level does not correlate with the severity of HE[9, 10] and it can be altered by many confounding factors[11].

The most common adverse effect is lactulose-induced diarrhea. About one-third of patients in both groups developed diarrhea which exceeded 4 times daily, but this was rapidly resolved after discontinuation of lactulose. Hypokalemia was seen in four cases of severe diarrhea but it was mild and easily corrected with oral potassium supplement. Other less common adverse effects are mild bloating, nausea, vomiting and abdominal pain which are similar to previous studies[6-8]. There is no serious adverse effect related to the study drugs.

Conclusion

Oral LOLA is safe but there is no add-on benefit for cirrhotic patients with overt HE who were treated with an optimal dose of lactulose. The most effective treatment in HE is to correct the precipitating factors, especially infection.

What is already known on this topic?

HE is a common complication in patients with cirrhosis. Lactulose is widely used for treating cirrhotic patients with overt HE. LOLA is effective for treatment of patients with mild HE compared with lactulose.

What this study adds?

LOLA is safe but it has no add-on benefit for treatment of patients with overt HE, combined with lactulose. The most effective treatment in overt HE is to correct the precipitating factors, especially infection.

Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Lizardi-Cervera J, Almeda P, Guevara L, Uribe M. Hepatic encephalopathy: a review. Ann Hepatol 2003; 2: 122-30.
2. Mas A. Hepatic encephalopathy: from pathophysiology to treatment. Digestion 2006; 73 (Suppl 1): 86-93.
3. Strauss E, Tramote R, Silva EP, Caly WR, Honain NZ, Maffei RA, et al. Double-blind randomized clinical trial comparing neomycin and placebo in the treatment of exogenous hepatic encephalopathy. Hepatogastroenterology 1992; 39: 542-5.
4. Tarao K, Ikeda T, Hayashi K, Sakurai A, Okada T, Ito T, et al. Successful use of vancomycin hydrochloride in the treatment of lactulose resistant chronic hepatic encephalopathy. Gut 1990; 31: 702-6.
5. Als-Nielsen B, Gluud LL, Gluud C. Non-absorbable disaccharides for hepatic encephalopathy: systematic review of randomised trials. BMJ 2004; 328: 1046.
6. Stauch S, Kircheis G, Adler G, Beckh K, Ditschuneit H, Gortelmeyer R, et al. Oral L-ornithine-L-aspartate therapy of chronic hepatic encephalopathy: results of a placebo-controlled double-blind study. J Hepatol 1998; 28: 856-64.
7. Kircheis G, Nilius R, Held C, Berndt H, Buchner M, Gortelmeyer R, et al. Therapeutic efficacy of L-ornithine-L-aspartate infusions in patients with cirrhosis and hepatic encephalopathy: results of a placebo-controlled, double-blind study. Hepatology 1997; 25: 1351-60.
8. Poo JL, Gongora J, Sanchez-Avila F, Aguilar-Castillo S, Garcia-Ramos G, Fernandez-Zertuche M, et al. Efficacy of oral L-ornithine-L-aspartate in cirrhotic patients with hyperammonemic hepatic encephalopathy. Results of a randomized, lactulose-controlled study. Ann Hepatol 2006; 5: 281-8.
9. Ong JP, Aggarwal A, Krieger D, Easley KA, Karafa MT, Van Lente F, et al. Correlation between ammonia levels and the severity of hepatic encephalopathy. Am J Med 2003; 114: 188-93.
10. Kramer L, Tribl B, Gendo A, Zauner C, Schneider B, Ferenci P, et al. Partial pressure of ammonia versus ammonia in hepatic encephalopathy. Hepatology 2000; 31: 30-4.

11. Stahl J. Studies of the blood ammonia in liver disease. Its diagnostic, prognostic, and therapeutic significance. Ann Intern Med 1963; 58: 1-24.
12. Prakash R, Mullen KD. Mechanisms, diagnosis and management of hepatic encephalopathy. Nat Rev Gastroenterol Hepatol 2010; 7: 515-25.
13. Guerit JM, Amantini A, Fischer C, Kaplan PW, Mecarelli O, Schnitzler A, et al. Neurophysiological investigations of hepatic encephalopathy: ISHEN practice guidelines. Liver Int 2009; 29: 789-96.
14. Randolph C, Hilsabeck R, Kato A, Kharbanda P, Li YY, Mapelli D, et al. Neuropsychological assessment of hepatic encephalopathy: ISHEN practice guidelines. Liver Int 2009; 29: 629-35.