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RESEARCH ARTICLE

ASSESSMENT OF EFFICACY OF L-ORNITHINE L-ASPARTATE IN CIRRHOTIC PATIENTS WITH ACUTE HEPATIC ENCEPHALOPATHY

Ayman M.E.M. Sadek[1], Osama A. Khalil[1], Monkez M. Yousif[1], M.S. Fawzi[2]

1 Internal Medicine Faculty of Medicine, Zagazig University, Egypt

2 Medical biochemistry Departments, Faculty of Medicine, Zagazig University, Egypt

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Corresponding Author

Ayman M.E.M. Sadek

Abstract

Background: Hepatic encephalopathy (HE) is a complication of impaired liver function and is manifested as neuropsychiatric signs and symptoms associated with acute or chronic liver disease in the absence of other neurological disorders. L-ornithine-L-aspartate (LOLA) is not frequently used for treatment of HE as there are still some reservations about its benefits. **Aim of the work:** To assess the effectiveness of LOLA either alone in high dose or combined with lactulose in regular dose versus lactulose alone in the management of advanced hepatic encephalopathy and their relation to the arterial blood ammonia level. **Methods:** Interventional randomized double blind clinical trial on sixty cirrhotic patients with hyperammonemia and overt hepatic encephalopathy grade III and IV according to West Haven criteria (WHC). Detailed history, clinical examination and investigations were done in addition to measurement of arterial blood ammonia level at admission, 24, 48 and 72 hours from admission. Patients were randomized to one of three treatment groups, group A (20 patients) received Lactulose alone (400 g/day given as retention enema), group B (20 patients) received high dose LOLA alone (40 g/day infused intravenously) and group C (20 patients) received Lactulose (400 g/day) plus regular dose LOLA (20 g/day); and they were followed up for 4 days of trial. **Results**: Thirty one patients (51.7%) had grade III HE while 29 patients (48.3%) had grades IV HE on admission. There was significant improvement in Glasgow Coma Scale (GCS) on the 3rd day in group B and C as compared to group A; and on the 4th day in group B as compared to group A and C and group C as compared to group A. There was significant improvement in Clinical Hepatic Encephalopathy Staging Scale (CHESS) on the 4th day in group B as compared to group A and C. There was significant improvement in ammonia level on the 2nd, 3rd and 4th days in group B and C as compared to group A. By the end of the trial full recovery occurred in 50% versus 35% versus 20% in group B, C and A respectively ($p < 0.05$). A Correlation coefficient showed significant positive correlation between arterial blood ammonia level with CHESS and significant negative correlation with GCS in the 2nd, 3rd, 4th days in all groups. **Conclusion:** Cirrhotic patients with advanced HE treated with high dose LOLA were associated with significant improvement of HE grade and lowering blood ammonia level than those on the other lines of treatment without appreciable side effects.

Introduction:

Hepatic encephalopathy (HE) is a well-recognized clinical complication of chronic liver disease. About 30% of patients with cirrhosis die from hepatic coma. The estimated incidence of hyperammonemic portal systemic encephalopathy is 26% at 5 years of cirrhosis diagnosis with a stepwise increase up to 70% in patients with poor liver function (Child-Pugh C).[1]

HE represents a broad continuum of neuropsychological dysfunction. As defined by the Working Party in 1998, HE can be categorized into 3 broad groups: type A, which occurs in acute liver failure (ALF); type B, which occurs in patients with bypass shunts; and the most commonly recognized form, type C, which occurs in patients with chronic liver disease.[2]

Fundamental conceptual advances in understanding of hepatic encephalopathy have confirmed the central role of ammonia in the pathogenesis of HE. [3] Ammonia is generated in the intestines from different sources: nitrogenous components of the diet, deamination of glutamine, and breakdown of urea by urease present in colonic flora. [4]

Glutaminase, the enzyme that metabolizes the deamination of glutamine, has been thought to play an important role in the pathogenesis of HE. [5] In the brain, glutaminase is located in the mitochondria of astrocytes and might be implicated in the toxic effects of ammonia in this organelle.[6]

The relative contribution of different organs highlights the role of skeletal muscle to buffer ammonia that is produced in the intestines and is not metabolized in the liver. [7] Liver cirrhosis with malnutrition has a higher incidence of encephalopathy. [8] Malnutrition incidence in liver cirrhosis ranges between 65-90%. This is partly the result of poor nutritional intake caused by encephalopathy and protein restriction. [9]

Metronidazole given in a 250-mg dose three or four times a day is as effective as oral neomycin and does not cause ototoxicity or nephrotoxicity. However, to avoid peripheral neuropathy, metronidazole therapy should not be extended beyond 2 weeks. Rifaximin has demonstrated to be as good as lactulose or lactitol for treatment of patients with hepatic encephalopathy. However, long term use of antibiotics raises concerns about bacteria resistance and high therapeutic costs for affected patients. [10]

Disaccharides such as lactulose or lactitol have a bacteriostatic effect, cathartic effects, and enhancement of conversion of ammonia to ammonium with excess hydrogen ion, then excreted into the feces and eliminated. [11] Side effects include initial bloating and flatulence and then severe diarrhea with dehydration and hyperglycemia and acidosis if the dosage is too high. [12]

LOLA has confirmed its efficacy in well designed controlled clinical trials, versus placebo. [13] LOLA stimulates the urea cycle and glutamine synthesis, which is an important mechanism in the detoxification of ammonia. [14] LOLA improves the ability of the liver and other organs to detoxify ammonia systematically in contrast to lactulose which acts locally in intestine. [15]

There are no adequate clinical trials comparing the efficacy of LOLA infusion against lactulose in patients with more severe hepatic encephalopathy. Therefore this study was designed to evaluate the efficacy of different treatment modalities in improvement of hepatic encephalopathy scales and their relation to serum ammonia level.

PATIENTS AND METHODS

This study was conducted on patients with hepatic encephalopathy grade III-IV according to West Haven criteria, who were admitted to the Medical Intensive Care Unit of Zagazig University Hospital, during the period from 1/09/2012 to 1/12/2013 as an interventional randomized double blind clinical trial with a primary outcome of sustained improvement of at least one grade in mental state based on the West Haven criteria during 1st 48 hours and a secondary outcome of decreased arterial blood ammonia levels over the 4 days of treatment.

A written informed consent was taken from the attendant (as the patients were unable to understand and sign consent due to advanced HE) before enrolment to the study and the protocol was approved by the Institution Revision Board (IRB) of the faculty of medicine, Zagazig University.

All patients with liver disease who were diagnosed as having hepatic encephalopathy secondary to liver cirrhosis and portal hypertension and classified as type C hepatic encephalopathy according to classification of hepatic encephalopathy. [2]

Hepatic encephalopathy is a diagnosis of exclusion. [16] Therefore, HE was diagnosed after excluding coma due to another causes include (acute stroke, hypoglycemic coma, medical poisoning, and respiratory failure).

Exclusion criteria were the precence of evidence of other neurological or psychiatric abnormality, serum creatinine greater than 3mg/dl, use of drugs affecting the central nervous system, alcohol withdrawal syndrome and patients with hepatic encephalopathy grade I and II according to WHC.

All the study personel were blinded to the treatment assignment for the duration of the study. The pharmaceutical supplier had no contact with the study participants. There was no restriction, blocking,or stratification of the randomization sequence.

The diagnosis and grading of hepatic encephalopathy being made on the basis of a detailed history, physical examination, WHC, GCS and CHESS. [11]

Inquiry was made about fever, GI bleeding, constipation, diarrhea, vomiting, diet and any trauma or surgery. The drug history, particularly, use of diuretics, sedatives or tranquilizers, and past history of hospital admission was also inquired.

The routine investigations carried out, which include full blood count, liver function tests, kidney function tests, coagulation profile, serum electrolyte, blood glucose, urine analysis, ascitic fluid examination in ascitic patients, chest radiograph. An abdominal ultrasound was done in all cases for liver size, parenchymal echogenicity, portal vein diameter, spleen size and for the detection of ascites. In the presence of ascites a diagnostic ascitic tap was also done to look for any evidence of spontaneous bacterial peritonitis.

The severity of liver disease was assessed on the 1st day by Child Pugh and MELD scoring systems [17]. All patients fall in class C according to Child Pugh score.

The specific investigations carried out in the form of arterial blood ammonia level measurement at admission before taking any medications and after 24, 48 and 72 hours. Venous ammonia sample was avoided as it was not ideal especially while assessing the role of LOLA which induce the urea cycle in muscles and may cause falsely reduced level of ammonia in venous sample that may have a potential of misinterpretation. A Beckman DB Spectrophotometer equipped Pith, a Hewlett-Packard 7101BM strip chart recorder and a cell compartment thermostated at 25.0+ 0.1º C was used for spectral measurements. Quartz cuvettes had 1.000 cm path lengths. Kartrell disposable polystyrene 1 cm cuvettes, Cat. No. 219, from Dynalab Corp., Rochester, NY, with a stated precision of ± 1%, was used for cycling assay measurements. In presence of glutamate dehydrogenase enzyme (GLDH), ammonia reacts with con l'α-ketogluterate and NADPH to form glutammate and NADP+. The absorbance decrease of NAPDH at 340 nm, due to its oxidation, defines the plasmatic ammonia concentration in the sample. Arterial blood was taken, with compression of the artery for 10 minutes, and centrifuged in a closed centrifuge tube as soon as possible, within maximum 15 minutes after collection. EDTA was used as anticoagulant. Ammonia (µg/dL) was calculated as the following: [ΔAS - (ΔABR x 0.83)] x 1633 were ΔABR (ΔA of Blank) = (Abr1-Abr2)-(Abr2-Abr3) and ΔAS (ΔA of Sample) = (As1-As2)-(As2-As3). Reference values were 25-94 µg/dL for men and 19-82 µg/dL for women. [18]

All patients underwent standard management during their ICU stay which included use of fluids, intestinal antiseptics such as metronidazole. Placement of a nasogastric tube for feeding was considered in all patients. All patients were randomized to three treatment groups and followed for 4 days:

- **Group A**: 200 g 20% Lactulose diluted with 700 ml water given as retention enema every 12 hours.
- **Group B:** Intravenous [IV] LOLA 40 g/day plus 1000 ml water retention enema every 12 hours.
- **Group C:** IV LOLA 20 g/day plus 200 g 20% Lactulose diluted with 700 ml water given as retention enema every 12 hours.

All patients were followed for the duration of 4 days by WHC, GCS, CHESS and fasting arterial blood ammonia level.

STATISTICAL ANALYSIS

IBM SPSS (Statistical package for social science) program version 20 for windows was used for data analysis. [19] Quantitative variables were summarized using Mean±SD. Chi square test and Fisher's exact test for categorical variables. Student's t-test was done to compare two parametric variables. Mann Whitney test for two non parametric variables. ANOVA (analysis of variance) for multiple parametric variables followed by POSTHOC test LSD (least significant difference). Kruskal-Wallis for multiple non parametric variables. Correlation coefficients (r) were calculated using the Pearson's correlation analysis. P value was significant at < 0.05 level and high significant at ≤ 0.001.

RESULTS

A total of 60 patients with cirrhosis and HE admitted to medical ICU were studied, of whom 42 (70%) were males, and 18 (30%) were females [Table 1]. Mean age was 58.62 ± 9.8 years [Table 2]. On admission, 31 (51.7%) patients had grade III HE while 29 (48.3%) had grades IV HE according to the WHC. The common comorbid conditions present were Diabetes mellitus in 9 (15%) and HCC in 5 (8.4%) [Table 3]. The most common precipitant of HE was infection in 20 (33.5%), gastrointestinal bleeding in 15 (25%), hypokalemia in 4 (6.7%), vomiting in 3 (5%), constipation in 3 (5%), diarrhea in 3 (5%), protein diet in 2 (3.3%), while no precipitant was noted in 15 (25%) patients [Table 4].

Significant improvement started to appear on the 3rd day according to WHC with full recovery was encountered on 4th day in 50% of patients in group B compared to 35% of patients in group C and 20% of patients in group A ($p < 0.05$) [table 5], 3rd day according to GCS [table 6], 4th day according to CHESS [table 7]. Significant difference in MELD score was founded between group A in comparison to group B and group C without significant difference between group B and group C [table 8]. Significant improvement started to appear on the 2nd day according to arterial blood ammonia level [table 9]. There was significant improvement in GCS on the 3rd day in group B and C as compared to group A; and on the 4th day in group B as compared to group A and C and group C as compared to group A. There was significant improvement in CHESS on the 4th day in group B as compared to group A and C. There was significant improvement in ammonia level on the 2nd, 3rd and 4th days in group B and C as compared to group A. Comparison of the delta value of arterial blood ammonia level between 1st and 4th days was done between the three groups to avoid bias that may result from unequal values on the 1st day and revealed significant lowering in group B and group C [table 10]. Correlation coefficient shows significant positive correlation between arterial blood ammonia level with CHESS and significant negative correlation with GCS in 2nd, 3rd, 4th days in all groups [table 11].

Table 1: Comparison of gender distribution in the different groups of study

			group			Total	X^2	P
			A	B	C			
Gender	F	Count	**7**	**6**	**5**	**18**	**0.47**	**NS**
		% within group	**35%**	**30%**	**25%**	**30%**		
	M	Count	**13**	**14**	**15**	**42**		
		% within group	**65%**	**70%**	**75%**	**70%**		
Total		Count	**20**	**20**	**20**	**60**		
		% within group	**100%**	**100%**	**100%**	**100%**		

Table 2: Comparison of age differences in the different groups of study

		N	Mean±SD	Minimum	Maximum	F	P
Age	group A	**20**	**58.75 ± 10.08**	**39**	**75**	**1.055**	**NS**
	group B	**20**	**60.8 ± 9.29**	**42**	**75**		
	group C	**20**	**56.3 ± 10.03**	**40**	**73**		

Table 3: Comparison of Co-morbidity distribution in the different groups of study

			group			Total	X^2	P
			A	B	C			
Co morbidity	Diabetes	Count	**2***	**3***	**3***	**8**	**6.04**	**NS**
		% within group	**10%**	**15%**	**15%**	**13.3 %**		
	Diabetes,HCC	Count	**1***	**0***	**0***	**1**		
		% within group	**5%**	**0.0%**	**0.0%**	**1.7%**		
	HCC	Count	**3***	**1***	**0***	**4**		
		% within group	**15%**	**5%**	**0.0%**	**6.7%**		
	None	Count	**14**	**16**	**17**	**47**		
		% within group	**70%**	**80%**	**85%**	**78.3 %**		
Total		Count	**20**	**20**	**20**	**60**		
		% within group	**100%**	**100%**	**100%**	**100%**		

*** Fisher's exact test** for frequencies less than 5

Table 4: The frequency of precipitating factors in the different groups of study

			group			Total
			A	B	C	
Precipitation	Bed sores	Count	**1**	**0**	**0**	**1**
		% within group	**5%**	**0.0%**	**0.0%**	**1.7%**
	Abdominal wall Cellulitis	Count	**0**	**1**	**0**	**1**
		% within group	**0.0%**	**5%**	**0.0%**	**1.7%**
	Lower limb cellulitis	Count	**0**	**0**	**1**	**1**
		% within group	**0.0%**	**0.0%**	**5%**	**1.7%**
	Chest infection	Count	**1**	**3**	**2**	**6**
		% within group	**5%**	**15%**	**10%**	**10%**
	Fever	Count	**0**	**0**	**1**	**1**
		% within group	**0.0%**	**0.0%**	**5%**	**1.7%**
	SBP	Count	**3**	**2**	**3**	**8**
		% within group	**15%**	**10%**	**15%**	**13.3%**
	SBP, Constipation	Count	**1**	**0**	**0**	**1**
		% within group	**5%**	**0.0%**	**0.0%**	**1.7%**
	SBP,Melena, Hypokalemia	Count	**1**	**0**	**0**	**1**
		% within group	**5%**	**0.0%**	**0.0%**	**1.7%**
	Vomiting	Count	**2**	**1**	**0**	**3**
		% within group	**10%**	**5%**	**0.0%**	**5%**
	Hematemesis	Count	**4**	**5**	**2**	**11**
		% within group	**20%**	**25%**	**10%**	**18.3%**
	Constipation	Count	**0**	**1**	**1**	**2**
		% within group	**0.0%**	**5%**	**5%**	**3.3%**
	Diarrhea	Count	**1**	**0**	**0**	**1**
		% within group	**5%**	**0.0%**	**0.0%**	**1.7%**
	Diarrhea, Hypokalemia	Count	**1**	**1**	**0**	**2**
		% within group	**5%**	**5%**	**0.0%**	**3.3%**
	Melena	Count	**0**	**0**	**3**	**3**
		% within group	**0.0%**	**0.0%**	**15%**	**5%**
	Hypokalemia	Count	**1**	**0**	**0**	**1**
		% within group	**5%**	**0.0%**	**0.0%**	**1.7%**
	Protein excess	Count	**0**	**1**	**1**	**2**
		% within group	**0.0%**	**5%**	**5%**	**3.3%**
	Not identified	Count	**4**	**5**	**6**	**15**
		% within group	**20%**	**25%**	**30%**	**25%**
Total		Count	**20**	**20**	**20**	**60**
		% within group	**100%**	**100%**	**100%**	**100%**

Table 5: Comparison of severity of HE by WHC between different groups in the 4 days

			group			Total	X^2	P
			A	B	C			
WHC day 1	Grade III	Count	**10**	**11**	**10**	**31**	**0.13**	**NS**
		% within group	**50%**	**55%**	**50%**	**51.7%**		
	Grade	Count	**10**	**9**	**10**	**29**		

	IV	% within group	**50%**	**45%**	**50%**	**48.3%**		
Total		Count	**20**	**20**	**20**	**60**		
		% within group	**100%**	**100%**	**100%**	**100%**		
WHC day 2	Fully conscious	Count	**1***	**2***	**2***	**5**	**5.6**	**NS**
		% within group	**5%**	**10%**	**10%**	**8.3%**		
	Grade I	Count	**2***	**4***	**1***	**7**		
		% within group	**10%**	**20%**	**5%**	**11.7%**		
	Grade II	Count	**5**	**3***	**6**	**14**		
		% within group	**25%**	**15%**	**30%**	**23.3%**		
	Grade III	Count	**4***	**7**	**5**	**16**		
		% within group	**20%**	**35%**	**25%**	**26.7%**		
	Grade IV	Count	**8**	**4***	**6**	**18**		
		% within group	**40%**	**20%**	**30%**	**30%**		
Total		Count	**20**	**20**	**20**	**60**		
		% within group	**100%**	**100%**	**100%**	**100%**		
WHC day 3	Fully conscious	Count	**3***	**5**	**6**	**14**	**19.4**	**<0.05 S**
		% within group	**15%**	**25%**	**30%**	**23.3%**		
	Grade I	Count	**3***	**5**	**1***	**9**		
		% within group	**15%**	**25%**	**5%**	**15%**		
	Grade II	Count	**0***	**5**	**4***	**9**		
		% within group	**0.0%**	**25%**	**20%**	**15%**		
	Grade III	Count	**2***	**4***	**4***	**10**		
		% within group	**10%**	**20%**	**20%**	**16.7%**		
	Grade IV	Count	**12**	**1***	**5**	**18**		
		% within group	**60%**	**5%**	**25%**	**30%**		
Total		Count	**20**	**20**	**20**	**60**		
		% within group	**100%**	**100%**	**100%**	**100%**		
WHC day 4	Fully conscious	Count	**4***	**10**	**7**	**21**	**18.4**	**<0.05 S**
		% within group	**20%**	**50%**	**35%**	**35%**		
	Grade I	Count	**2***	**6**	**2***	**10**		
		% within group	**10%**	**30%**	**10%**	**16.7%**		
	Grade II	Count	**1***	**2***	**2***	**5**		
		% within group	**5%**	**10%**	**10%**	**8.3%**		
	Grade III	Count	**0***	**1***	**2***	**3**		
		% within group	**0.0%**	**5%**	**10%**	**5%**		
	Grade IV	Count	**13**	**1***	**7**	**21**		
		% within group	**65%**	**5%**	**35%**	**35%**		

Total	Count	**20**	**20**	**20**	**60**		
	% within group	**100%**	**100%**	**100%**	**100%**		

*** Fisher's exact test** for frequencies less than 5

Table 6: Comparison of severity of HE by GCS between different groups in the 4 days

	Mean ± SD			F	P
	Group A	Group B	Group C		
GCS day 1	**8.2 ± 3.94**	**8.5 ± 2.93**	**8.15 ± 3.65**	**.057**	**NS**
GCS day 2	**9.65 ± 4.9**	**11.3 ± 3.01**	**10.45 ± 4.25**	**.799**	**NS**
GCS day 3	**8.45 ± 4.15**	**13.25 ± 2.67 a**	**11.2 ± 4.57 a**	**6.627**	**<0.05 S**
GCS day 4	**7.55 ± 3.4**	**14.1 ± 2.36 a**	**11.1 ± 4.77 ab**	**11.218**	**<0.001 HS**

a = Significant difference in comparison to group A
b = Significant difference in comparison to group B

Table 7: Comparison of severity of HE by CHESS between different groups in the 4 days

	Mean ± SD			F	P
	Group A	Group B	Group C		
CHESS day 1	**8.25 ± 1.12**	**8.45 ± .61**	**8.45 ± .61**	**.404**	**NS**
CHESS day2	**6.55 ± 2.95**	**5.95 ± 2.54**	**6.15 ± 3.15**	**.197**	**NS**
CHESS day3	**6.45 ± 3.83**	**3.9 ± 3.09**	**4.9 ± 3.87**	**Z = 2.528**	**NS**
CHESS day4	**6.15 ± 4.12**	**1.95 ± 2.76 a**	**4.65 ± 4.25 b**	**Z = 6.375**	**<0.05 S**

a = Significant difference in comparison to group A
b = Significant difference in comparison to group B

Table 8: Comparison of severity of liver disease by MELD score between different groups of study in the 1st day

	Mean±SD			F	P
	Group A	Group B	Group C		
MELD	**26.3±7.69**	**20.3±5.32 a**	**19.2±4.97 a**	**7.8**	**0.001 HS**

a = Significant difference in comparison to group A

Table 9: Comparison of arterial blood ammonia level (µg/dL) between different groups of study in the 4 days

	Mean ± SD			F	P
	Group A	Group B	Group C		
Arterial Ammonia day 1	**431.85 ± 298.11**	**332.69 ± 221.66**	**313.69 ± 243.75**	**Z=1.224**	**NS**
Arterial Ammonia day 2	**295.03 ± 213.98**	**180.78 ± 128.36 a**	**189.15 ± 114.94 a**	**Z=3.224**	**<0.05 S**
Arterial Ammonia day 3	**270.02 ± 221.35**	**140.26 ± 96.4 a**	**160.94 ± 114.19 a**	**Z=4.089**	**<0.05 S**
Arterial Ammonia day 4	**316.36 ± 283.49**	**105.51 ± 90.3 a**	**151.76 ± 116.57 a**	**Z=7.217**	**<0.05 S**

a = Significant difference in comparison to group A

Table 10: Comparison of the DELTA value of arterial blood ammonia level (µg/dL) between 1st and 4th day between different groups of study

	Mean of delta ± SD			KW	P
	Group A	Group B	Group C		
Arterial Ammonia (µg/dl) day1-day4	**115.4 ± 265.6**	**227.1 ± 180.9 a**	**161.9 ± 243.6**	**6.12**	**0.042**

a = Significant difference in comparison to group A

Table 11: Correlation coefficient between arterial Ammonia levels (µg/dL) versus different HE scales in the 4 days

	GCS day1		**CHESS day1**	
	r	p	r	p
Arterial ammonia day1	**-.018-**	**.894 NS**	**.171**	**.191 NS**
	GCS day2		**CHESS day2**	
Arterial ammonia day2	**-.312-***	**.015 S**	**.272***	**.035 S**
	GCS day3		**CHESS day3**	
Arterial ammonia day3	**-.503-****	**.000 HS**	**.475****	**.000 HS**
	GCS day4		**CHESS day4**	
Arterial ammonia day4	**-.573-****	**.000 HS**	**.548****	**.000 HS**

** Correlation is significant at the 0.01 level (2-tailed).
*.Correlation is significant at the 0.05 level (2-tailed)

DISCUSSION

This was a head to head comparison trial evaluating the efficacy of high I.V. LOLA dose versus lactulose retention enema versus combined lactulose retention enema and low I.V. LOLA dose in the management of sever hepatic encephalopathy.

All patients in the present study showed evidences suggesting cirrhosis either clinical, laboratory or ultrasonographic evaluation. High resolution ultrasongraphic analysis of the liver surface is a reliable non invasive test for diagnosis of cirrhosis**.** [20]

Males were dominant in the present study, and a similar finding was observed in a retrospective study of hepatic encephalopathy in Pakistan**.** [21] Male predominance may be explained by the higher prevalence of HCV among male**.** [22]

The present study shows that the most common comorbid conditions present was, Diabetes in 15% of patients. This was in agreement with **Mumtaz et al., 2010** [23]**,** who found that, the common comorbid conditions in patients with HE, was Diabetes mellitus in 41% of patients. Because diabetes mellitus (DM) may be associated with delayed gastrointestinal transit, which cause an increased ammonia level of gut bacterial origin, so its presence in patients with cirrhosis would predispose to and exacerbate HE. [24]

Infections were identified as the main precipitant of HE in this study in up to 33.5% of patients, with around 16.7% of patients suffering from SBP, 10% suffering from chest infection, 3.4% from cellulites, 1.7% from bed sores and 1.7% with fever of unknown origin. This may be the reflection of bad nutritional status and hygienic conditions of our patients. Strict dietary restrictions on cirrhotic patients lead to anorexia and malnutrition, and eventually lowering their immunity and making them more susceptible to infections**.** [25] Infection may predispose to impaired renal function and to increased tissue catabolism, both of which increase blood ammonia levels**.** [26] This was in agreement with, study done in Pakistan by **Mumtaz et al., 2010** [23], who reported that Infection was identified as the main precipitant of HE in up to 35% of patients; and by **Abid et al.,2011**[27] who reported that infection reaches 44.9% of patients. However, studies done in USA by **Souheil et al., 2001**[28] found infections responsible in only 3% of cases. Also Literature from other developed countries has not identified infections as amongst the most common precipitating events, possibly due to more awareness and better nutrition status in their patients**.** [29]

GI bleeding in our patients was the second precipitating factor for HE. It was identified in 25% of patients. This was in agreement with, **Bustamante et al., 1999** [30]**,** who reported that, GI bleeding was the second precipitating factor. GI bleeding precipitating HE by, impairment in liver function due to hepatic hypoperfusion and increase in the production of ammonia and other nitrogenous substances in the gut**.** [31]

Hypokalemia (K < 3.5 mmol/L) was found in 6.7% of patients. Hypokalemia can contribute to the development, or worsen the symptoms, of hepatic encephalopathy. Hypokalemia precipitating HE by increasing renal production of ammonia**.** [32] This was in agreement with, **Abid et al., 2011**[27] who reported that 10% had hypokalemia and, **Alam et al., 2005** [33] who reported that 18% had hypokalemia.

Five percent of patients had constipation; this may be due to, low fiber diet, and lack of physical activity by our patients. It causes HE by increasing ammonia production and absorption. This was in agreement with study done in Pakistan by **Zakaria et al., 2008**[34]**,** who reported that, constipation considered a precipitating factor in 7% of patients. **Abid et al., 2011**[27] reported a much higher figure reaching 21.7% of patients had constipation.

The intake of large amount of protein diet was also a precipitating factor found in the present study in 3.3% patients, due to lack of guidance regarding nutritional supplements for our patients. Similar conclusion was made by **Devrajani et al., 2009.** [35]

Although, the current study shows that no precipitating factors could be identified in 25% of patients, this was found in the study conducted by **Abid et al., 2011**[27] who reported that 26.7% of patients had unidentified precipitating factors. On the other hand, **Maqsood et al., 2006**[21] reported a much lower figure that 9% of patients had unidentified precipitating factors.

The present study was aiming to assess the effectiveness of LOLA either alone in high dose or combined with lactulose in regular dose versus lactulose alone in the management of advanced hepatic encephalopathy and their relation to the arterial blood ammonia level. Despite the short period of treatment trial, the primary outcome (sustained improvement of at least one grade in mental state based on the West Haven criteria during 1st 48 hours) was achieved in; 30% of the patients in group A with a 20% full recovery of conscious level at the end of treatment trial; 90% of the patients in group B with a 50% full recovery of conscious level at the end of treatment trial; and 55% of the patients in group C with a 35% full recovery of conscious level at the end of treatment trial. The

secondary outcome (decreased arterial blood ammonia levels over the 4 days of treatment) was achieved in 85% of the patients in group A; 95% of the patients in group B; and 80% of the patients in group C. **Ashoor et al., 2012**[36] conducted a previous randomized clinical trial in the same location with a conclusion that patients who received I.V. branched chain amino acids plus LOLA demonstrated lower blood ammonia levels with shorter ICU stay time. A recent meta-analysis study, **Bai et al., 2013**[37] concludes that, LOLA benefits both overt and minimal HE patients in the improvement of HE by reducing the serum ammonia concentration compared with the placebo/no-intervention control. Also; another recent meta-analysis study by **Ahuja et al., 2014**[38] concludes that, LOLA in a doses range from 9-18g orally or 20g IV/day improved symptoms of clinically overt encephalopathy relative to either lactulose or placebo. **Abid et al., 2011**[27], founds IV LOLA 20g/day to be safe and improves hepatic encephalopathy as adjuvant compared to placebo, especially in higher grade of encephalopathy, Also **Abdo-Francis et al., 2010**[39]**,** founds that treatment with LOLA was more effective than lactulose in improving HE. **Jiang et al., 2009**[40] **and Soárez et al., 2009**[41] conducted a critical analysis of studies assessing LOLA in HE treatment in a doses range from 5g to 40g IV/day with a conclusion that LOLA is effective in reducing hyperammonemia of HE, which was accompanied by improvement of the psychometric tests especially with high dose 40g/day. **Ahmad et al., 2008**[42] showed that LOLA infusions in a dose of 20g IV/day resulted in greater improvement in postprandial ammonia and mental state grade than placebo; also, LOLA was safe and well-tolerated, Finally **Poo et al., 2006**[43] were comparing LOLA 9-18g orally versus lactulose 30-60ml orally and patients randomized to both therapeutic groups showed a significant decrease in serum ammonia levels. However, only patients in the LOLA- treatment group had a significant improvement in Mental Status, Number Connection Test, asterixis, and EEG activity, and consequently a significant global improvement in the portosystemic encephalopathy index. Furthermore, patients treated with both study drugs reported an improvement in quality of life, according to the Visual Analogue Scale of the EuroQol Survey. This improvement was significantly greater in patients who received LOLA.

Alberto et al., 2010[44]**,** on the contrary, concluded that the combined therapy of lactulose/l-ornithine l-aspartate did not show significant results compared with only lactulose when assessing clinical improvement and the reduction of ammonia levels after 7 days. It can be explained by the low dose of LOLA used in this study 9g daily and the oral route which may affect the bioavailability of the drug. Also; **Acharya et al., 2009**[45] study showed that LOLA infusion (30g/day) for 3 days does not improve survival or reduce complications and is ineffective in lowering the ammonia levels in patients with acute liver failure (ALF). It may be due to the fundamental difference between the interorgan ammonia trafficking in ALF and cirrhosis. In cirrhosis, there is some remaining liver cell mass that retains some capacity to detoxify ammonia. In ALF, the capacity for urea synthesis is severely decreased, and renal failure is frequent.

The patients tolerated the high I.V. dosage of LOLA without appreciable side effects compared to other groups.

Further trial for assessment of long term efficacy and safety of high systemic dosage of LOLA in patients with advanced HE is necessary.

In conclusion precipitant-induced hepatic encephalopathy is a common complication of cirrhosis. Infections and gastrointestinal bleeding were identified as the major precipitants in this study. There was a significant positive effect of high dose LOLA 40g/day alone and to a lesser extent combined treatment of lactulose with regular dose of LOLA 20g/day on both clinical improvement of high grade hepatic encephalopathy grade III & IV and reduction of arterial blood ammonia level when compared with lactulose treatment alone.

CONFLICT OF INTEREST

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