Precipitating Factors and Hospital Outcome of Hepatic Encephalopathy In Cirrhotic Patients at Tertiary Centre in Egypt

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ABSTRACT: Background: Hepatic encephalopathy (HE) is a common clinical manifestation of advanced liver disease and/or portosystemic shunt and is manifested clinically by neuropsychiatric signs and symptoms in absence of other neurological disorders. **Aim of the work:** Determination of precipitants of hepatic encephalopathy and effect of different treatment regimens, and their impact on ICU stay and mortality in patients with liver cirrhosis. **Patients and Methods:** Within eight months period from *November* 2009 to *June* 2010, 540 patients with established liver cirrhosis manifesting signs of HE were admitted to our Internal Medicine ICU. Patients were randomized to receive four treatment regimens; Standard treatment (ST) only (intravenous fluids, lactulose and metronidazole along with retention enema), ST plus branched chain amino acids (BCAA), ST plus L-Ornithine-L-aspartate (LOLA) and ST plus LOLA plus BCAA. **Results:** Of the 540 cirrhotic patients, 353 (65.4%) were males, and 187 (34.6%) were females. Mean age of participants was (61 ± 8.4 years). Hepatitis C virus was the main cause of liver cirrhosis in 465 patients (86.1%), hepatitis B in 20 patients (3.7%) and non-B, non-C cirrhosis was seen in 55 patients (10.2%). 489 (90.6%) patients had Child-Pugh class C, 51 (9.4%) patients had class B, while no patients had Child class A. On admission, 5.4% patients had grade 1 HE while 30.4%, 41.5% and 22.4% had grades 2, 3 and 4 respectively. The most common precipitants of HE were; infection in 159 patients (29.4%), gastrointestinal bleeding in 146 patients (27%), constipation in 47 patients (8.7%).No precipitant was found in 40 patients (7.4%). Old age, hemodynamic instability, Child-Pugh class C, grades 3 or 4 HE, renal impairment, recurrent episodes of HE and sepsis were independent factors for high ICU mortality. Mean ICU stay was (2.54 ± 1days), shorter ICU stay was associated with grade 1, 2 HE, Child class B, and treatment group IV (BCAA plus LOLA), while, longer ICU stay was associated with grade 3, 4 HE and Child-Pugh class C. In standard treated group, mean ICU stay was (2.97±1.1 days) vs. (2.1±0.9 days) in the group treated with BCAA plus LOLA. In the group treated with standard treatment, ICU mortality was 36% vs. 15.4% in the group treated with BCAA plus LOLA. **Conclusion:** Infections and gastrointestinal bleeding were the major precipitants for HE in our study. Patients with old age, hemodynamic instability, grades 3 or 4 HE, renal impairment, and recurrent episodes of HE on admission were associated with worse hospital outcomes. Intravenous infusion of LOLA and BCAA accelerate HE recovery, improve hospital outcome and reduce overall ICU mortality.

1. Introduction

Hepatic encephalopathy (HE) is a clinical syndrome frequently observed in patients with liver cirrhosis, it represents a variable clinical spectrum of neuropsychiatric manifestations that may proceed to hepatic coma. About 30% of cirrhotic patients presented with HE die in hepatic coma. [1]

HE occurs as a squally of extensive liver diseases either acute or chronic. The most common causes of chronic hepatic diseases in Egypt are viral hepatitis that includes chronic viral hepatitis C (HCV) and chronic hepatitis B (CHB). [2]

HE presents in two forms, acute and chronic. The acute form is usually associated with fulminated hepatic failure and can rapidly progress to seizures, coma and even death. [3]

In majority of patients with established liver cirrhosis, acute HE is most commonly associated with precipitating factors while recurrent HE can occur with or without a precipitating factor and is usually easily reversible. [4]

In many cases of HE, a precipitating factor can be usually identified and treatment of HE episode is usually directed towards correction of this precipitant. Once the precipitating condition has been resolved, the encephalopathy is usually also subsides. [5]

The most common precipitants identified for HE are GI bleeding and Infection. [6] Infections such as urinary tract infection, chest infection and spontaneous bacterial peritonitis are the most frequent recorded infections. [7] Other precipitants include constipation, excessive dietary protein, hypovolemia, hypokalemia and alkalosis. Medications centrally acting on the CNS like opiates and benzodiazepine have been also implicated in precipitation of HE. [8]

The main objectives in treatment of HE are fourfold; provision of supportive care, correction of any precipitating factors, reduction of the nitrogen

load in the gastrointestinal tract and last, to assess the need for long-term therapy for prevention of recurrence of HE. [9]

The primary objective of this study was aimed at evaluating the common precipitating factors of HE and their frequency in cirrhotic patients. Other secondary objectives were to evaluate the efficacy of different treatment regimens, and their impact on hospital stay and mortality.

2. Patients and Methods

Study design and setting:

This prospective observatory study was conducted during the period from *November* 2009 to *June* 2010 on 540 cirrhotic patients with HE who was admitted to internal medicine ICU of Zagazig University hospitals, Sharqya governorate, Egypt.

Target population and sampling:

Patients included in this study showed evidence of decompensated liver cirrhosis, which was confirmed with clinical evaluation, laboratory testing and real time abdominal ultrosongraphic examination. The severity of liver cirrhosis was assessed through Child-Pugh score system (Table 1). The diagnosis and grading of HE were based on detailed history, physical examination and West Haven criteria. [11]

Exclusion criteria:

Patients with disturbed level of consciousness or coma due to other causes were excluded from the start. Similarly, patients with acute stroke, hypoglycemic coma, medical poisoning and respiratory and renal failure were also excluded.

Table (1): Child-Pugh score [10]

Parameters	Numerical score		
	1	2	3
Ascites	Non	Slight	Moderate
HE	Non	Grade I-II	Grade III-IV
Bilirubin	< 2mg/dl	2-3 mg/dl	>3 mg/dl
Albumin	>3.5 g/dl	2.8-3.5 g/dl	<2.8 g/dl
PT (prolonged)	<4 sec.	4-6 sec.	> 6 sec.

Patient's classification and randomization:

Patients included in this study received standard treatment (ST) during their ICU stay that included, intravenous fluids, intestinal antiseptics and gut cleansing agents, which included lactulose and metronidazole along with retention enema until HE improved. Placement of a nasogastric tube for feeding was considered in all patients with HE grades 3&4. Our patients were randomized- according to their treatment regimens- into four different groups:

Group I: included *150* patients and received ST only.

Group II: included 130 patients and received ST plus injectable branched chain amino acids (BCAA) (Aminoleban injectable-*Otsuka Egypt Ldt*) in a dose of 0.5-1 L per day.

Group III: included 130 patients and received ST plus injectable L-Ornithine-L-aspartate (LOLA)(Hepa -Merz ampoules-*MERZ,Germany*) in a dose of 4 to 8 ampoules per day .

Group IV: included *130* participants and received ST, BCAA plus LOLA.

All patients were followed during their ICU stay for hospital outcomes. Recovery time from HE and ICU mortality were recorded and enlisted.

Patients included in this study were submitted to:

- Full history taking and clinical inquiry from patient's relatives about fever, GI bleeding, constipation, diarrhea, vomiting, diet patterns and any past history of head trauma or surgery. The drug history, particularly use of diuretics, sedatives or tranquilizers, and past history of hospital admissions were also inquired.
- Routine investigations that included; complete blood count, serum bilirubin, albumin, creatinine and blood urea, coagulation profile and PT, serum electrolytes, blood glucose, urine analysis and ascitic fluid examination.
- Abdominal ultrasound for assessment of liver size and hepatic parenchymal echogenicity, portal vein diameter, splenic size and for detection of ascites if any. In presence of ascites, a diagnostic ascitic tap was done to look for analysis and any evidence of spontaneous bacterial peritonitis.

Statistical analysis:

Statistical analysis was performed using Statistical Package for Social Science version 14 (SPSS Inc., New York, NY). Descriptive analysis of patients with HE was performed for demographic and laboratory parameters and results were presented as mean ± standard deviation (SD) for quantitative variables. For comparison of proportions chi-square test was applied and p value equal or less than 0.05 was considered as significant.

3. Results

During a period of eight months, 540 consecutive cirrhotic patients with HE were admitted to our ICU. The mean age of patients was 61 ± 8.4 years. Sex distribution among patients showed that 353 (65.4%) were males and 187 (34.6%) were females.

On looking to HE grading, we recorded 29 (5.4%) patients were in grade 1, 166 (30.4%) in grade 2, 224 (41.5%) in grade 3 and 121 (22.4%) in grade 4 HE. Regarding the frequency of HE, we reported 82 (15.2%) patients had first episode of HE, 195 (36.1%) had second episode of HE, and 263 (48.7%) had recurrent episodes of HE.

The most common comorbid conditions associated with liver cirrhosis in our study were; DM

in 210 patients (38.9%), HCC in 100 patients (18.5%) and renal impairment in 64 patients (11.9%).

Table (2): Demographics data of participants.

Variables	No.	%
Sex:		
Male	353	65.4
Female	187	34.6
Age (Years):		
< 60	175	32.4
> 60	365	67.6
Grade of HE:		
I	29	5.4
II	166	30.7
III	224	41.5
IV	121	22.4
Precipitating factors:		
Present	500	92.6
Unidentified	40	7.4
HCC :		
Present	100	18.5
Absent	440	81.5
Renal Impairment:		
Present	68	12.6
Absent	472	87.4
Diabetes mellitus:		
Present	210	38.9
Absent	330	61.1
Child's classification:		
A	0	0
B	51	9.4
C	489	90.6
Number of the attacks:		
First	82	15.2
Second	195	36.1
Recurrent	263	48.7
Hepatitis Markers:		
HCV	465	86.1
HBV	20	3.7
No hepatitis markers	55	10.2
Group o treatment:		
I	150	31.5
II	130	22
III	130	24.5
IV	130	22

According to Child Pugh's score, 51 patients (9.4%) were found to have Child Pugh's class B, 489 patients (90.6%) had Child Pugh's class C. No patients were found to have Child class A. Mean Child Pugh's score was (12.7 ± 1.8).

Regarding hepatitis markers, chronic HCV infection was detected in 465 patients (86.1%) while, chronic HBV was found in 20 patients (3.7%). No hepatitis markers (B or C) were detected in 55 patients (10.2%)*(Tables 2).*

Different precipitants of HE were identified in 500 of 540 patients (92.6%), while, no detectable precipitants were found in 40 patients (7.4%). The most common precipitant identified in our study was infection that was reported in 159 patients (29.4%) [SBP in 78 patients (49%), chest infection in 54 patients (33.1%), UTI in 16 patients (10%) and cellulites in 11 patients (6.9%)]. The second most common precipitating factor for HE in our study was upper gastrointestinal (GI) bleeding, which was

reported in 146 patients (27%). The third common precipitating factor was constipation in 47 patients (8.7%), diarrhea in 45 patients (8.3%), diuretics in 35 patients (6.4%), vomiting in 25 patients (4.6%), excess protein intake in 18 patients (3.3%), sedatives in 15 patients (2.7%), tapping of ascites in 6 patients (1.1%) and post-surgery HE was recorded only in 4 patients (0.7%) *(Tables 3).*

Table (3): Frequency of precipitants of HE.

Precipitating Factor	No.	%
Infections:	**159**	**29.4**
SBP	78	49
Chest	54	33.1
UTI	16	10
Cellulites	11	6.9
GI Bleeding	**146**	**27**
Constipation	**47**	**8.7**
Diarrhea:	**45**	**8.3**
With low K	39	86.7
With normal K	6	13.3
Diuretics:	**35**	**6.4**
With low K	32	91.4
With normal K	3	8.6
Vomiting:	**25**	**4.6**
With low K	18	72
With normal K	7	28
Excess protein intake	**18**	**3.3**
Sedatives	**15**	**2.7**
Tapping:	**6**	**1.1**
With low K	3	50
With normal K	3	50
Post-surgery	**4**	**0.7**
No precipitant	**40**	**7.4**
Total number	**540**	**100**

Total ICU mortality rate in our study was 123 patients (22.7%). Causes of death were as follow: septic shock in 26 patients (21.1%), HRS in 28 patients (22.7%), end-stage liver disease with multiple organ failure without evidence of sepsis in 33 patients (26.8%) and uncontrolled GI bleeding in 36 patients (29.2%)*(Tables 4).*

ICU mortality was significantly affected by patient's age. It was more frequent in elderly patients > 60 year. High mortality rate was also recorded in hemodynamic unstable patient at the time of admission if they had severe liver disease (Child C classification). Also, high ICU mortality was associated with comorbidities like DM, renal impairment and HCC. Moreover, grade 3 and 4 HE and recurrent HE were also associated with high ICU mortality **(Table 4).**

The mean duration of ICU stay was (2.5 ± 1 day), ranging from 1 day to 6 days. Shorter ICU stays (i.e. early recovery) was associated with grade 1, 2 HE, Child class B, and treatment group IV (BCAA plus LOLA), whereas, longer ICU stay (i.e. late recovery) was associated with grade 3, 4 HE, Child class C and patients of group 1 treated with ST **(Table 5).**

Table (4): Factors affecting ICU mortality.

Factor		Dead No.	Dead %	Alive No.	Alive %	Total No.	Total %	χ^2	P value
Age :	< 60 y	30	17.5	141	82.4	171	32.4	3.9	<0.05
	> 60 y	93	9.5	276	66.2	369	67.6		
Hemodynamic:	- Stable	50	11.8	374	88.2	424	78.5	135.4	<0.001
	- Unstable	73	62.9	43	37.1	116	21.5		
HCC :	- Present	35	35	65	65	100	18.5	10.4	<0.001
	- Absent	88	20	352	80	440	81.5		
RI :	- Present	25	36.7	43	63.3	68	12.6	10.95	<0.001
	- Absent	98	20.7	374	79.3	472	87.4		
DM:	-Present	64	30.5	146	69.5	210	38.8	11.5	<0.001
	-Absent	59	17.8	271	82.1	330	61.2		
No. Of attack	1st	10	12.9	67	87.1	77	14.3	12.16	<0.05
	2nd	36	18.1	163	81.9	199	36.8		
	Recurrent	77	29.2	187	70.8	264	48.9		
CP classification:	- B	5	9.8	46	90.2	51	9.4	5.39	<0.05
	- C	118	24.2	371	75.8	489	90.6		
Grade of HE	- I	0	0	29	100	29	5.4	133.6	<0.001
	- II	6	3.6	160	96.4	166	30.7		
	- III	47	20.9	177	79.1	224	41.5		
	- IV	20	57.8	51	42.2	121	22.4		
Treated groups :	- I	54	36	96	64	150	27.8	21.43	<0.001
	- II	26	20	104	80	130	24.07		
	- III	23	17.7	107	82.3	130	24.07		
	- IV	20	15.4	110	84.6	130	24.07		

Table (5): Factors affecting the length of ICU stay in alive patients.

Variable		Length of ICU stay (Alive) Mean ± SD (days)	Range (days)	T value	P value
Age :	- < 60 y	2.3 ± 0.73	(1 - 6)	2.3	NS
	- > 60 y	2.5 ± 0.48	(1 - 6)		
Hemodynamic state:	Stable	2.56 ± 1	(1 - 6)	1.15	NS
	Unstable	2.44 ± 1	(1 - 6)		
NO. of attack:	1st	2.5 ± 0.9	(1 - 6)	0.58	NS
	2nd	2.5 ± 0.98	(1 - 6)		
	Recurrent	2.6 ± 1.05	(1 – 6)		
Grade of HE:	- I	1 ± 0.2	(1 - 2)	238.9	<0.001
	- II	2.01 ± 0.4	(1 - 4)		
	- III	2.8 ± 0.5	(1 - 6)		
	- IV	3.6 ± 0.5	(1 - 6)		
Group of treatment:	- I	2.76 ± 0.8	(1 - 6)	12.23	<0.001
	- II	2.7 ± 0.76	(1 - 6)		
	- III	2.6 ± 0.67	(1 - 5)		
	- IV	1.82 ± 0.5	(1 - 6)		
Child's classification	- B	2.42 ± 1	(1 - 6)	2.22	< 0.05
	- C	2.75 ± 0.9	(1 - 6)		
HCC :	- Present	2.5 ± 0.8	(1 - 6)	1.1	NS
	- Absent	2.3 ± 0.8	(1 - 6)		
Renal impairment:	- Present	2.76 ± 0.85	(1 - 6)	2.01	NS
	- Absent	2.4 ± 0.8	(1 - 6)		

4. Discussion

Hepatic encephalopathy (HE) describes unique neuropsychiatric symptoms that occur in patients with acute and/or chronic liver diseases in absence of other neurological disorders. [12] In majority of patients with HE, a clearly defined precipitating factor usually is identified, and reversal or control of these factors is a key step in management of HE. [15]

Chronic HCV infection was the main cause of liver cirrhosis in our study (about 81% of all patients). This result is not surprising in a country like Egypt where, the national prevalence of HCV infection may reach about 22% of the general population in some governorates. [13] Our result is slight near to that of EL-Shadway *et al.,* [20] who reported a slight similar result (24%) in our governorate. Our finding agrees with that of *El-Zanaty et al.,* [13] who reported that Egypt has the highest seropositivity of HCV infection worldwide and that chronic long standing HCV infection is responsible for about 80 % of all cirrhotic patients in Egypt. Worldwide, similar studies were done in Pakistan and showed that about 70% of cirrhotic patients presented with HE suffered from chronic HCV infection. [14&15] However, studies coming from industrialized nations had shown that chronic alcohol consumption is the main etiological factor for chronic liver disease and liver cirrhosis followed by chronic HCV infection. [16]

The most common comorbid disease recorded in our study was DM. DM was detected in 38.9% of our cirrhotic patients. DM is usually associated with delayed gastrointestinal transit time, which may theoretically increases ammonia production from gut bacteria. [18] Therefore, presence of DM in patients with liver cirrhosis would predispose them to and exacerbate HE in those patients. Moreover, DM may adversely affect the course of chronic viral infection and is eventually associated with increase liver steatosis and fibrosis that may eventually increases prevalence of HCC. [19] Our finding is similar to that of *Mumtaz K et al.,* [15] who recorded 41% of cirrhotic patients have DM. In the same way, *Sigal et al.,* [18] confirmed that diabetic patients with HCV induced – liver cirrhosis have more sever HE than non-diabetic and is usually associated with poor global hospital outcomes. Moreover, we noticed that ICU mortality was significantly higher in diabetic cirrhotic patients than non- diabetic ones.

Infection-*mainly SBP*- was identified as the main precipitant of HE in 29.4% of our patients. This relative high percentage of infection predisposition in our cirrhotic patients with HE may reflect the bad nutritional status of these patients. Faulty dietary instructions and protein restriction from patient's relatives, paramedical personals and even doctors may lead to anorexia, malnutrition that eventually lower patient's immunity making them more susceptible to infections. [21] *Mumtaz K et al.,* [15] reported slightly higher percentage (35%) of infection among their series. In the opposite side, studies from developed countries have not identified infection amongst the most common precipitating factors, possibly due to more awareness and better nutrition status of their patients. [22] Recurrent untreated infections in cirrhotic patients intensely predispose them to impaired renal function and to increased tissue catabolism, both of which increase blood ammonia levels. [23]

Ingestion of large amount of animal protein diet was another precipitating factor for HE in our study in about 3.3% of our patients. This may be related to lack of patient's guidance regarding nutritional supply as mentioned above. *Bikha R. et al.,* [27] made a similar conclusion but with slightly low percentage (1.5%) in his study on the precipitants for HE in cirrhotic patients. Although, avoiding intake of large amounts of protein may be advantageous for reducing the levels of protein-dependent GI toxins, faulty protein restriction may worsen liver function and even increases risk of death, while, a positive nitrogenous balance may improve HE by promoting hepatic regeneration and increasing the capacity of the muscles to detoxify ammonia. [28]

Cirrhotic patients often have portal hypertension and usually presented with upper or/and lower GI bleeding that may lead to transient hepatic decompensation. [29] In our study, GI bleeding was the second most common precipitating factor for HE (next to infection), as it was identified in 27% of our patients. Our reported results agree with *Bustamante et al.,* who reported a similar result (23%). [24]

Sedation during upper and/or lower GI endoscopy is usually needed in cirrhotic patients eligible for diagnostic or therapeutic endoscopies for patient's compliance and ease of the procedure. [30] Midazoalm is the commonest and preferable drug used to achieve preendoscopic conscious sedation in most of our endoscopic units and it may aggravate subclinical HE (SHE), especially in Child B&C cirrhotic patients. Endoscopic sedation was a precipitating factor in only 2.7% of our patients. Our results are so near to that of *Bikha et al.,* (3%) [27], *Assy et al., (4%)* [31] and *Cagnin et al., (2.5%).* [39] In the other side, our result is far from that of *Fichet J et al.,* (35%) [33] and *Benhaddouch et al.,* (33.3%). [34] Sedation with propofol has a shorter time of recovery and discharge than midazolam and does not exacerbate subclinical HE in cirrhotic patients, so recent reports and guidelines recommend propofol as a standard drug for achievement of preendoscopic sedation. [32]

Table (6): Studies showing frequencies of HE precipitants in cirrhotic patients.

Study	GI bleeding (%)	Infection (%)	Constipation (%)	Low K (%)	Protein Diet (%)
Souheil (2001)	18	3	3	11	9
Khurram (2001)	31	11	33	7	13
Alam (2005)	24	22	32	18	4
Saad (2006)	38	24	8	12	12
Our study (2010)	27	29.4	8.7	17	3.3

Hyponatremia (Na < 130 mmol/L) is a common laboratory finding in patients with liver cell failure and is usually associated with ascites. Hyponatremia may cause low grade cerebral edema, which is an important factor in the pathogenesis of HE in cirrhotic patients [25]. In our study, hyponatremia was detected in 223 (41.3%) patients. Moreover, hypokalemia (K < 3.5 mmol/L) was found in 92 (17%) patients. Hypokalemia and hyponatremia can contribute to development and/or worsening of HE. [26] *Alam et al., 2005* [14] reported that electrolytes imbalance was found in 56% of cirrhotic patients with HE, among of them, 38% of patients had hyponatremia, while 18% of patients had hypokalemia.

In many patients with advanced liver cirrhosis who have low hepatic reserve, no precipitants can be detected. [24] This is usually accounted in Child's C cirrhotic patients that actually predispose patients for development of spontaneous HE even in absence of any offender or participant. [35] In our study, no precipitating factors were identified in 7.4% of our patients. *Saad et al.,* [17] reported a slight similar result (10%).

When, we compared the frequencies of different precipitating factors in four different international studies with our results, we found that infection and GI bleeding were the most common precipitating factor in our study and in most of these studies (Table 6). While, our results match one study done in Pakistan by *Saad et al.,* 2006 [17], another two Pakistani studies revealed that GI bleeding and constipation were the main precipitating factors for HE in cirrhotic patients *(Khurram et al., 2001* [35] *and Alam et al., 2005* [14]*)*. However, studies from USA *(Souheil et al., 2001* [36]*)* showed that GI bleeding and hypokalemia were the most common precipitating factors for HE, while, infection and constipation were the least common precipitating factors for HE in predisposed cirrhotic patients.

The total number of deaths recorded in our study during ICU stay was 123 out of 540 patients (22.8 %).ICU mortality was significantly changed in different treated groups; ICU mortality was 36% in group 1, 20% in group 2, 17.5% in group 3 and15.4% in group 4. These results are so near to *Bikha et al., 2009*, who reported near identical result (23%). [27] Our results are slight far from that of *Fichet J et al., 2009,* (35%) [33] and *Benhaddouch et al., 2007,* (33.3%). [34]

In our study, ICU mortality was significantly affected with patient age, hemodynamic stability (on admission), severity of liver disease, comorbidities (DM, renal impairment and HCC), HE grading (on admission), Child's class, serum albumin, serum bilirubin, prothrombin time, serum sodium and number of HE episodes.

On correlating HE grading in relation to ICU mortality in our study, we found that more ICU mortality was found in patients with grade 3 &4 HE at the initial hospital presentation. This finding is in complete harmony with tow studies done by *Saad et al.,* 2006, [17] and *Bikha et al., 2009* [27] who reported similar results.

Hemodynamic instability at the time of ICU admission significantly increases mortality in our patients. *Fichet J et al.,* 2009[33], also reported this finding and added that systolic hypotension (less than 90 mmHg) at the time of hospital admission was strongly associated with high ICU mortality. [37] In the same direction, ICU mortality-in our study- was significantly high in patients with hyponatremia. This finding was also reported and published in two separated series by *Fernandez-Esparrach et al.,* in 2001 [38] and *Fichet J et al., in 2009.* [33]

The mean duration of ICU stay in our study was (2.5 ± 1) days, ranging from 1 day to 6 days. Shorter ICU stays (i.e. early recovery) was associated with grade 1,2 HE, Child's class B, and treatment group IV (BCAA plus LOLA), while, longer ICU stay (i.e. late recovery) was associated with grade 3, 4 HE, Child's class C, and treatment group I (standard treatment). Same conclusions were confirmed and published by other authors. [40, 41, 42&43]

BCAAs may have a therapeutic role in treatment of HE by improving regional cerebral blood flow in patients with liver cirrhosis. [45] In a large multicenter, randomized trial on patients with liver cirrhosis, intravenous infusion BCAAs was found to improve both rate of death and progression to liver failure [46].

In our study, patients received BCAAs alone (group II) or with LOLA (group IV) have been demonstrated to have lower blood ammonia levels in comparison to other groups (I&III). Moreover, on comparison of ICU stay time among our groups, we found that patients treated with BCAA plus LOLA (group IV) had the shortest ICU stay time in comparison to other groups.

The total ICU stay for reversal of HE after administration of BCAA plus LOLA was (1.82 ± 0.5) day vs. (2.76 ± 0.8) day in patients under standard treatment. This results may related to the ability of BCAA to provide substrates needed for intracellular conversion of ammonia to urea and glutamine in liver and kidney leading to decrease blood ammonia level and subsequently minimizing HE and decreasing ICU stay period. [43&44]

Treatment with BCAA plus LOLA may have a very promising role in early reversal of HE in cirrhotic patients. Naylor et al., [47] conducted a meta-analysis study in 1989 on cirrhotic patients suffered from HE who received BCAA plus LOLA and estimate the mean time needed for reversal of HE and concluded that mental recovery in patients with HE was rapid, moreover, Afzal et al., in 2010 [41] added that more duration of treatment was required in patients given standard treatment for reversal of HE as compared to patients who were given BCAAs plus LOLA through I.V. route.

Although, our results agree with that of Ahmad et al., (2008) [48], Jiang et al., (2009) [47] and Abdo-Francis et al., (2010) [42] who reported that treatment with BCAAs plus LOLA were more effective than lactulose in improving HE and reducing the duration of hospital stay, however, Soárez et al., (2009) [51] found that no sufficient data for evidence of beneficial effect of BCAAs plus LOLA on cirrhotic patients with HE. Moreover, some randomized controlled trials failed to confirm the efficacy of BCAAs plus LOLA in treatment of hepatic encephalopathy. [49] More randomized trials may be needed before verification that intravenous infusion of LOLA and BCAAs should be a routine treatment option for all cirrhotic patients presented with HE.

4. Conclusion

- Precipitant-induced HE is a common clinical manifestation of liver cirrhosis. Infections, GI bleeding and constipation were identified as the major precipitants in our study.
- Once the precipitating condition is resolved, HE also typically disappears. Elderly patients, hemodynamic instability on admission, grades 3 or 4 HE, renal impairment and recurrent episodes of HE on admission were associated with worse ICU outcomes.
- Shorter ICU stays was associated with grade 1, 2 HE, Child class B, and treatment by BCAA plus LOLA.
- Patients treated with BCAA and LOLA in addition to standard treatment had lower ICU mortality.

5. References

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