STUDY OF PRECIPITATING FACTORS AND HOSPITAL OUTCOME OF HEPATIC ENCEPHALOPATHY PATIENTS WITH PRECIPITANTS

By

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ABSTRACT

Background: Hepatic encephalopathy is a complication of impaired liver functionand is manifested as neuropsychiatric signs and symptoms associated with acute or chronic liverdisease in the absence of other neurological disorders. The main objective of this study was to determine precipitants of hepatic encephalopathy (HE) and different treatment regimens, and their impact on ICU stay and mortality.

Methods:from November 2009 to June 2010, 540 patients with cirrhosis of liver, manifesting signs ofhepatic encephalopathy (HE) were included. Detailed history, clinical examination and thorough investigations were doneto look for any precipitating factor.All patients were randomized to four treatment groups, standard treatment, branched chain amino acids (BCAA), L-Ornithine-L-aspartate (LOLA) and BCAA plus LOLA.

Results: Of the 540 patients 353 (65.4%) were males, and 187 (34.6%) were females. Mean age was 61 ± 8.4 years. Hepatitis C virus was the cause of cirrhosis in 465 (86.1%); Child-Pugh (C-P) class C was present in 489 (90.6%) patients. On admission, 5.4% patients had grade 1 HE while30.4%, 41.5% and 22.4% had grades 2, 3 and 4 respectively. The most common precipitant of HE was infection in 159 (29.4%), gastrointestinal bleeding in 146 (27%), constipation in 47 (8.7%) patients,while no precipitant was noted in 40 (7.4%) patients.Twenty-three percent died during ICU stay. Univariateanalysis identified old age, hemodynamic instability, grades 3 or 4 HE, renal impairment, recurrent episodes of HE and sepsis associated with ICU mortality. Mean ICU stay was 2.54 ± 1days. Shorter ICU stays (i.e. early recovery) was associated with grade 1, 2 HE, Child class B, and treatment group IV (BCAA plus LOLA). Longer ICU stay (i.e. late recovery) was associated with grade 3, 4 HE, Child class C, and treatment group I (standard treatment).In the group treated with standard treatment, mean ICU stay was2.97±1.1 days vs. 2.1±0.9days in the group treated with BCAA plus LOLA.In the group treated with standard treatment, ICU mortalitywas 36%vs. 15.4% in the group treated with BCAA plus LOLA.

Conclusion: Infections, gastrointestinal bleeding were identified as the major precipitants in this study. Patients with old age, hemodynamic instability, grades 3 or 4 HE, renal impairment, and recurrent episodes of HE on admission was associated with worse outcomes. Shorter ICU stays (i.e. early recovery) was associated with grade 1, 2 HE, Child class B, and treatment group IV (BCAA plus LOLA). Patients treated with group IV, which include BCAA and LOLA, had early recovery and lower mortality.

Keywords: Hepatic encephalopathy. Cirrhosis. Hepatitis C. Precipitant. Outcome.

INTRODUCTION

Hepatic encephalopathy (HE) is a syndrome observedin patients with cirrhosis. It is defined as a spectrum ofneuropsychiatric abnormalities in patients with liverdysfunction, after exclusion of other known causes of braindisease. About 30% of patients with cirrhosis die in hepatic coma [(1)]

HE occurs as a complication of advanced liver disease, either chronic or acute. [(2)]Egypt has the highest prevalence of antibodies to hepatitis C virus (HCV) in the world, estimated nationally at 14.7%. An estimated 9.8% are chronically infected.[(3)]Ammonia is produced in the gastrointestinal tract by bacterial degradation, it adversely affect brain function and play a role in HEpathogenesis. [(4)]

A precipitatingfactor can be usually identified, and the treatment of theepisode is directed towards the correction of thisprecipitant. Once the precipitating

condition has beenresolved, the encephalopathy also subsides usually.[5] The most common precipitant identified is gastrointestinalbleeding, which is responsible for up to 34%cases of HE.[6] Gastrointestinal bleeding contributes approximately 20 grams of proteins per 100 ml of blood,leading to an increased production of nitrogenousproducts especially ammonia from the gut.[7]

Infection may predispose to impaired renal function and to increased tissue catabolism, both of which increase blood ammonia levels.[8]Various infections such as urinary tract, chest and spontaneous bacterial peritonitis are frequent causes of morbidity in cirrhosis, including the development of HE.[9]Otherprecipitants include constipation, excessive dietaryprotein, especially animal protein hypovolemia, shock,hypokalemia and alkalosis.[10]Use of medications actingon the CNS such as opiates and benzodiazepine,presence of infections and shunt procedures have alsobeen implicated in the precipitation of HE.[11]

The main objectives in the treatment of HE are fourfold: (1) provide supportive care, (2) correct any precipitating factors, (3) reduce the nitrogen load in the gastrointestinal tract, and (4) assess the need for long-term therapy.[8]

This study was aimed at evaluating thecommon precipitating factors and their frequency inpatients presenting with HE. Other objectives were to evaluate different treatment regimens, and their impact on hospital stay and mortality.

PATIENTS AND METHODS

This study was conducted on 540 patients with hepatic encephalopathy, who were admitted to the medical intensive care unit of Zagazig University Hospital during the period from November 2009 to June 2010.

All patients showed evidences of chronic liver disease by clinical, laboratory testingand ultrasonographic evaluation. The severity of liver cirrhosiswasassessed through Child-Pugh score system[12](Table 1)

Table (1): Child-pugh score

Parameters	Numerical score		
	1	2	3
Ascites	Non	Slight	Moderate to severe
Encephalopathy	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 (seconds > control)	<4 sec.	4-6 sec.	> 6 sec.

Allpatients with liver disease who were diagnosed as having HE secondary to liver cirrhosis and portalhypertension and classified as type C HE according toclassification of HE by Fereci et al.[11]

Hepatic encephalopathy is a diagnosis of exclusion. [13] Therefore, HE was diagnosed after excluding coma due to another causes include (acute stroke, hypoglycemic coma, medical poisoning, and respiratory failure).

The diagnosis and grading of HE being madeon the basis of a detailed history, physicalexamination, and West Haven criteria.[11]

Inquiry was made about fever, GI bleeding, constipation, diarrhea, vomiting, diet and anytrauma or surgery. The drug history, particularly, use ofdiuretics, sedatives or tranquilizers, and past historyof 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, ascetic fluid examination, chest radiograph.An abdominal ultrasound was done in all casesfor liver size, parenchymal echogenicity, portal veindiameter, spleen size and for the detection of ascites. Inthe

presence of ascites a diagnostic ascitic tap was alsodone to look for any evidence of spontaneous bacterialperitonitis.

All patients underwent standard management during their ICU stay which included use of fluids, intestinal antiseptics and gut cleansing agents such as lactulose and metronidazole, along with retention enema until HE improved. Placement of a nasogastric tube for feeding was considered in all patients with HE grade > 2. All patients were randomized to four treatment groups.

Group I: standard treatment

Group II: standard treatment+ BCAA

Group III: standard treatment+ LOLA

Group IV: standard treatment + BCAA plus LOLA

All patients were followed for the durationof their stay in the ICU and whether they survived ordied at the end of the stay was recorded.

STATISTICAL ANALYSIS

Statistical analysis was performed using the StatisticalPackage for Social Science (SPSS).Descriptiveanalysis of patients with hepatic encephalopathy wasperformed for demographic and laboratory parametersand results presented as mean ± standard deviation forquantitative variables.For comparison of proportions chi-square test was applied and p value equal or less than 0.05 was considered as significant.

RESULTS

A total of 540 patients with cirrhosis and HE admitted to medical ICU were studied, of whom 353 (65.4%) were males, and 187 (34.6%) were females. Mean age was 61 ± 8.4 years. There were 465 (86.1%) patients with cirrhosis due to hepatitis C infection, while 20 (3.7%) had hepatitis B, non-B, non-C cirrhosis was seen in 55 (10.2%) patients. They were classified according to Child Pugh's score, 51 (9.4%) patients had class B, and 489 (90.6%) patients had class C. Mean child score was 12.7 ± 1.8.

Twenty nine (5.4%) patients were in grade 1, while 166 (30.4%) had grade 2, 224 (41.5%) grade 3 and 121 (22.4%) had grade 4 HE on presentation based on the West Haven criteria. Eighty two (15.2%) had first episode of HE, while 195 (36.1) had second episode of HE, and 263 (48.7) had recurrent episode of HE. The common comorbid conditions present were Diabetes mellitus in 210 (38.9%),renal impairment in 64 (11.9%) and HCC in 100 (18.5%).other demographic parameters are shown in Table 2.

Different precipitants of HE were identified in 500/540 (92.6%) patients while none could be found in 40 (7.4%) patients. The most common precipitant identified was, infection which was seen in 159 (29.4%) patients {SBP in 78 (49%), chest infection in 54 (33.9%), UTI in 16 (10%) and cellulites in 11 (6.9%)}. The second common precipitating factor was upper gastrointestinal bleeding in 146 (27%) patients, The third common precipitating factor was constipation in 47 (8.7%) patients, then diarrhea in 45 (8.3%) patients, diuretics in 35 (6.4%) patients, vomiting in 25 (4.6%) patients, excess protein in 18 (3.3%) patients, sedatives in 15 (2.7%) patients, tapping of ascites in 6 (1.1%) patients, and post surgery in 4 (0.7%) patients.(Table 3)

Table (2):Demographics parameters of all patients with HE.

Variables		No.	%
Sex	**male**	353	65.4
	female	187	34.6
Age	**< 60 years**	175	32.4
	> 60 years	365	67.6
Grade of HE:	- I	29	5.4
	- II	166	30.7
		224	41.5
	- III	121	22.4
	- IV		
Precipitating factor:	**- present**	500	92.6
	- unidentified	40	7.4
HCC :	**- present**	100	18.5
	- absent	440	81.5
RI :	**- present**	68	12.6
	- Absent	472	87.4
Diabetes :	**- present**	210	38.9
	- absent	330	61.1
Child's Pugh classification:	**- A**	0	0
	- B	51	9.4
	- C	489	90.6
No. of the attack :	**- first**	82	15.2
	- second	195	36.1
- recurrent		263	48.7
Group of treatment :	**- I**	150	31.5
	- II	130	22
	- III	130	24.5
	- IV	130	22

The ICU mortality rate was 22.7% (123 of 540 patients), Deaths were due to septic shock (n = 26, 21.1%), HRS (n = 28, 22.7%) or end-stage liver disease or multiple organ failure without evidence of sepsis (n = 33, 26.8%), and Uncontrolled GI bleeding (n = 36, 29.2%)

In this study ICU mortality was significantly affected with: age> 60 year, hemodynamic instability, severity of liver disease (more mortality with child C), comorbidities (as diabetes mellitus, renal impairment and HCC), the grade of hepatic encephalopathy (more mortality with grade 3 and 4), number of episode of HE (more mortality with recurrent episodes of HE),and serum albumin, serum bilirubin, prothrombin time, serum sodium (More mortality with prolonged PT, hyperbilirubinemia, hpoalbuminemia, and hyponatremia). (Table 4)

Table (3):Frequency of precipitating factors of patients with HE

Precipitating Factor	No.	%
Infection (SBP, chest, UTI, cellulites):	**159**	**29.4**
SBP	78	49
Chest	54	33.9
UTI	16	10
Cellulites	11	6.9
GI Bleeding	**146**	**27**
Constipation	**47**	**8.7**
Diarrhea:	**45**	**8.3**
With hypokalemia	39	86.7
With normal K level	6	13.3
Diuretics:	**35**	**6.4**
With hypokalemia	32	91.4
With normal K level	3	8.6
Vomiting:	**25**	**4.6**
With hypokalemia	18	72
With normal K level	7	28
Excess protein	**18**	**3.3**
Sedatives	**15**	**2.7**
Tapping:	**6**	**1.1**
With hypokalemia	3	50
With normal K level	3	50
Post surgery	**4**	**0.7**
No factor	**40**	**7.4**
Total number of patients	**540**	

In the present study, 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). Longer ICU stay (i.e. late recovery) was associated with grade 3, 4 HE, Child class C, and treatment group I (standard treatment). (Table 5)

Table (4):Factors affecting MICU mortality

Factors		Dead No.	Dead %	Alive No.	Alive %	Total No.	Total %	χ^2	P value
Age:-	< 60 y	30	17.5	141	82.4	175	32.4	3.9	<0.05
	> 60 y	93	29.5	276	66.2	365	67.6		
Hemodynamic:	Stable	50	11.7	374	88.2	424	78.5	135.4	<0.001
	unstable	73	62.9	43	37	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	63.2	68	12.6	10.95	<0.001
	- Absent	98	20.7	374	79.2	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	77	14.2	12.16	<0.05
	2nd	36	18.1	163	81.9	199	36.8		
	Recurrent	77	29.2	187	70.8	264	48.9		
C-P classification:	- B	5	9.8	46	90.1	51	9.4	5.39	<0.05
	- C	118	24.1	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	96.3	166	30.7		
	III	47	20.9	177	79	224	41.5		
	IV	70	57.8	51	42.1	121	22.4		
Treatment groups	I	54	36	9664		15027.8		21.43	<0.001
	II		2620	104	80	13024.07			
	III		2317.7	10782.3		13024.07			
	IV		2015.4	110	84.6	130	24.07		

Table (5): factors affecting the length of MICU 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 impairement :	-present	2.76 ± 0.85	(1 - 6)	2.01	NS
	- absent	2.4 ± 0.8	(1 - 6)		
Diabetes :	- present	2.6 ± 0.98	(1 - 6)	0.48	NS
	- Absent	2.5 ± 1	(1 - 6)		

DISCUSSION

The syndrome of hepatic encephalopathy (HE) describes all neuropsychiatric symptoms occurring in patients with acute or chronic liver diseases (CLD) in the absence of other neurological disorders. (14)

This study was conducted on 540 patients with hepatic encephalopathy, who were admitted to the medical intensive care unit of Zagazig University Hospital during the period from November 2009 to June 2010.

The main objective of this study was to determine precipitants of hepatic encephalopathy (HE) and different treatment regimens, and their impact on ICU stay and mortality.

This study was conducted on 540 patients with hepatic encephalopathy, who were admitted to the Medical Intensive Care Unit of Zagazig University Hospital during the period from 1/11/2009 to 30/6/2010.

All patients in our study showed evidences suggesting cirrhosis either clinical, laboratory or ultrasonographic evaluation.

Regarding the degree of hepatic dysfunction, 9.4 % were Child's class B and 90.6 % were Child's class C cirrhosis. It is a logical expectation as HE is mostly related to degree of hepatic dysfunction. Almost similar results were found in the study ofAlam et al., (2005).(15)

In our study, the majority of patients were HCV positive; this was in agreement with El-Zanaty F et al., 2009,(16) who found that, Egypt has the highest prevalence of antibodies to hepatitis C virus (HCV) in the world, estimated nationally at 14.7%. The number of Egyptians estimated to be chronically infected was 9.8%. Studies done in Pakistan were showed that 70% of patients with HE, suffered from hepatitis C(17). Whereas studies done in industrialized nations of the west, had shown that, alcohol as the main etiological factor. (18)

We found that majority of the patients were more than 60 years of age, this reflect the long course of the prevalent cause of liver disease in Egypt i.e. HCV. About gender, the male were dominant in our study, and a similar finding was observed in a retrospective study of hepatic encephalopathy in Pakistan by Saad et al., 2006.(19)Male predominance may be explained by the higher prevalence of HCV among male. (20)

We found that the most common comorbid conditions present was, Diabetes in (38.9%) patients. This was in agreement with, Mumtaz K et al., 2010,(17) who found that, the common comorbid conditions in patients with HE, was Diabetes mellitus in (41%) 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 HCV-related cirrhosis would predispose to and exacerbate HE. (21)

In our study infection was identified as the main precipitant of HE in up to 29.4% patients, with around 49% patients suffering from SBP, 34% suffering from chest infection, 10.1% from urinary tract infection, and 6.9% from cellulites. 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. (22) Infection may predispose to impaired renal function and to increased tissue catabolism, both of which increase blood ammonia levels. (23)

This was in agreement with, study done in Pakistan by Mumtaz K et al., 2010,(17) who reported that Infection was identified as the main precipitant of HE in up to 35% patients. In contrast study from 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. (24)

In our study GI bleeding was the second precipitating factor; it was identified in 27% patients. This was in agreement with, Bustamante et al., (1999),[25] 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. [26]

In our study 8.7% 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 Manzar Z et al., 2008,[27] who reported that, constipation considered a precipitating factor in 7% patients.

In our study, hyponatremia (Na < 130 mmol/L) was found in 223 (41.3%) patients. Hyponatremia, is a common complication in patients with advanced cirrhosis and ascites, it may cause low-grade cerebral edema as a result of swelling of astrocytes, which is an important element in the pathogenesis of HE in cirrhotic patients. [28]In our study, hypokalemia (K < 3.5 mmol/L) was found in 92 (17%) patients, among them, 39 patients had associated diarrhea, 18 patients had vomiting, 32 patients were on diuretics and 3 patients had undergone large volume paracentesis. Hypokalemia can contribute to the development, or worsen the symptoms, of hepatic encephalopathy. Hypokalemia precipitating HE by increasing renal production of ammonia. [29]This was in agreement with, Alam et al., 2005 [15] who reported that, Electrolyte imbalance, was found in (56%) patients with HE. Among them, (38%) patients had hyponatremia (Na < 130 mmol/L) while (18%) had hypokalemia (K < 3.5 mmol/L).

The intake of large amount of protein diet was also a precipitating factor found in our study in 3.3% patients, due to lack of guidance regarding nutritional supplements for our patients. Similar conclusion was made by Bikha R. et al., 2009.[30]Although avoiding intake of large amounts of protein may be advantageous for reducing the levels of toxins involved inHE, restriction may worsen liver function and increase the risk of death. A positive nitrogenous balance may improve encephalopathy by promoting hepatic regeneration and increasing the capacity of the muscle to detoxify ammonia. For these reasons the current recommendation is to avoid restrictions of dietary protein. [31]

Sedatives were considered in patients who developed HE after endoscopy for upper GI bleeding under midazolam sedation. In our study sedatives was a precipitating factor in 2.7% patients, this was in agreement with Assy N. et al., 1999[32] who reported that, sedation with midazolam for upper GI endoscopy exacerbates hepatic encephalopathy.Midazolam is a benzodiazepine, cirrhotic patient has poor ability to clear benzodiazepine like compounds. Such compounds bind to the GABA receptor complex inducing GABA release and neuroinhibition. [33]Midazolam sedation for upper gastrointestinal (GI) endoscopy exacerbates HE in patients with liver cirrhosis, therefore an alternative drug regimen for these patients is warranted. Sedation with propofol has a shorter time recovery and a shorter time to discharge than midazolamand does not exacerbate sub-clinical hepatic encephalopathy in cirrhotic patients. [34]

Post tapping was considered in patients who develop HE after large volume abdominal paracentesis (≥ 10 liters).in our study large volume paracentesis was a precipitating factor in 1.1% patients, due to hypovolemia and electrolytes disturbance, this was in agreement with Manzar Z et al., 2008[27] who reported that, large volume paracentesis

was considered a precipitating factor in 1.3% patients.

In our study, no precipitating factors could be identified, in (7.4%) patients. This was in agreement with, Saad et al., 2006[19] who reported that (10%) of patients had unidentified precipitating factors. In patients with low reserves of hepatic function, the hepatic encephalopathy can be a chronic condition and no precipitants can be established. The low reserve predisposes the patient to development of spontaneous hepatic encephalopathy.

Table (6): The findings of the frequencies of different precipitating factors in different international studies are given in this table

Studies	GI bleed %	Infection %	Constipation %	Hypokalemia %	Large 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	44	38	12	12
Present study (2010)	27	29.4	8.7	17	3.3

It can be accessed from the above table that, our findings, infection and GI bleeding were the most common precipitating factors, match those studies done in Pakistan (Saad, 2006).[19]Whereas other studies from Pakistan reveal gastrointestinal bleeding and constipation as the main precipitating factors (Khurram 2001, Alam 2005).[35,15] However studies from USA (Souheil, 2001)[36] showed that, GI bleeding and hypokalemia were the most common precipitating factors, but infection and constipation were a less precipitating factor of HE.

In our study, the total number of deaths during the period of ICU stay was 123 (22.8 %). Deaths were due to septic shock (21.2%), HRS (22.8%) or uncontrolled bleeding (29.2%),and end-stage liver disease (26.8%). This was in agreement with the study of Fichet J et al., 2009,[37] who found that patients with HE had a (35%) ICU mortality rate. Deaths were due to septic shock (36%), HRS (12%) or ARF (8%), end-stage liver disease or multiple organ failure without evidence of sepsis (24%), and bleeding complications (12%).Also Benhaddouch et al., 2007,[38] found that MICU mortality rate in patients with HE, was (33.3%) and seemed higher in gastrointestinal bleeding. And Bikha R. et al., 2009,[30] found that mortality rate was (23%). In this study ICU mortality was significantly affected with: age of the patients, hemodynamic stability, severity of liver disease (determined by Child-Pugh classification), comorbidities (as diabetes mellitus, renal impairment and HCC), the grade of hepatic encephalopathy (on admission), serum albumin, serum bilirubin, prothrombin time, serum sodium, and number of episode of HE.

As regard Grade of hepatic encephalopathy: more mortality with grade 3 and 4 of HE, this is in complete harmony with the study done by Saad et al., 2006,[19] who stated that higher mortality rates, associated with grades 3 and 4 of HE. As regard the significant increase in ICU mortality associated with Child's class C, this was in agreement with Bikha R. et al., 2009,[30] who mentioned that mortality was 23% and the majorities were Class C.As regard the significant increase in ICU mortality associated with hemodynamic instability, this was in agreement with Fichet J et al., 2009[37] who found that hypotension at the time of admission was strongly associated with mortality.

In this study ICU mortality was significantly associated with hyponatremia; this was in agreement with Fernandez-Esparrach et al.,

2001[39]) who found that, hyponatremia in patients with advanced cirrhosis, has been correlated with increased mortality. Hyponatremia and impaired solute-free water excretion are well-recognized events in the cascade leading to hepatorenal syndrome and ascites, and have been associated with increased liver-related mortality. [40]

In our study, ICU mortality was significantly associated with renal impairment, this was in agreement with Fichet J et al., 2009[37] who reported that renal failure (ARF or HRS) at any time was also associated with an increased mortality.

Also mortality was significantly associated with diabetes, this was in agreement with Sigal SH et al., 2006[41] who found that, Diabetic patients with HCV cirrhosis have more severe HE, and associated with poor outcome.DM may adversely affect the course of chronic hepatitis C and be associated with increase liver steatosis and fibrosis and may show an increased prevalence of hepatocellular cancer.[42]In this study mortality was significantly associated with HCC, this was in agreement with Yoneyama K et al., 2004[43] who reported that HCC predict a poor outcome in patient with hepatic encephalopathy.

In the present study, the mean duration of ICU stay was 2.5 ± 1 day, ranging from 1 day to 6 day.Shorter ICU stays (i.e. early recovery) was associated with grade 1, 2 HE, Child class B, and treatment group IV (BCAA plus LOLA). Longer ICU stay (i.e. late recovery) was associated with grade 3, 4 HE, Child class C, and treatment group I (standard treatment).

As regard grade of HE, longer ICU stay with grade 3 and 4 HE, this was in agreement with Mumtaz K et al., 2010 [17] who reported that, longer hospital stay in patients with grades 3 or 4 HE. As regard severity of liver disease, longer ICU stay with Child C, this was in agreement with Mumtaz K et al., 2010 [17] who reported that, longer hospital stay, ≥ 4 days, in patients with Child C.

In this study, patients were classified into four treatment groups according to different treatment regimens. The four regimens were as follows: standard treatment, branched chain amino acids (BCAA), L-Ornithine-L-aspartate (LOLA) and BCAA plus LOLA.

In our study patients received treatment group II, are given Branched chain amino acids which include valine, isoleucine and leucine. The high concentrations of branched chain amino acids (e.g. leucinc, isoleucine and valine) and low concentrations of aromatic amino acids (phenylalanine, tryptophan, tyrosine, methio-ninc) is effective in decreasing GABA levels in brain that is a inhibitory neurotransmitter, causing improvement in hepatic encephalopathy. [46]In our study patients received treatment group III, are given L-Ornithine-L-aspartate. LOLA has been demonstrated to reduce blood ammonia levels by providing substrates for theintracellular conversion of ammonia to urea and glutamine. [47]

This study has shown that BCAA plus LOLA have a very promising role in early reversal of hepatic encephalopathy and reduces the duration of ICU stay as compared to patients given standard treatment (i.e. Lactulose and Metronidazole). The total duration for reversal of hepatic encephalopathy after giving (BCAA plus LOLA) was 1.82 ± 0.5 vs. 2.76 ± 0.8 in patients under standard treatment.

This was in agreement with Naylor et al., (1989)[48] who conducted a meta-analysis suggested that mental recovery in patients with HE, was rapid in treated patients with BCAA infusion. And Afzal et al., (2010)[44] who reported that more duration of treatment was required in patients given standard treatment i.e., Lactulose and Metronidazole, for reversal of hepatic encephalopathy as compared to patients given branched chain amino acids through I/V route. However,

some randomized trials failed to confirm the efficacy of BCAAs in treatment of hepatic encephalopathy [(50)].Also this was in agreement with Abdo-Francis et al., (2010)[(45)], who reported that, treatment with LOLA was more effective than lactulose in improving HE and reducing the duration of hospital stay. And Jiang et al., (2009)[(48)] who reported that, LOLA infusions were found to be effective in cirrhotic patients with hepatic encephalopathy. However Soárez et al., (2009)[(51)] found that no sufficient evidence of a significant beneficial effect of LOLA on patients with hepatic encephalopathy.

In this study mortality was significantly affected with the treatment groups. In the group received standard treatment (group I), ICU mortality was 36% vs. 15.4% in the group received BCAA plus LOLA (group IV). So lower mortality associated with treatment group IV.

CONCLUSION

Precipitant-induced hepatic encephalopathy is a common complication of cirrhosis. Infections, gastrointestinal bleeding and constipation were identified as the major precipitants in this study. Once the precipitating condition is resolved the encephalopathy also typically disappears. Patients with old age, hemodynamic instability, grades 3 or 4 HE, renal impairment, and recurrent episodes of HE on admission was associated with worse outcomes.Shorter ICU stays (i.e. early recovery) was associated with grade 1, 2 HE, Child class B, and treatment group IV (BCAA plus LOLA). Patients treated with group IV, which include BCAA and LOLA, had early recovery and lower mortality.

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