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Original Article

Role of Sustained Low-Efficiency Dialysis (SLED) in Hyperammonia Patients with Hepatic Encephalopathy

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Abstract

Objective: To assess the role of sustained low-efficiency dialysis (SLED) in patients with hyperammonia secondary to liver failure.

Methods: In this retrospective study, 20 patients with hepatic encephalopathy from hyperammonia secondary to liver failure (14 with ACLF and 6 with ALF) were offered SLED. The study excluded pediatric patients and those with normal ammonia or without hepatic encephalopathy. Data collected included demographics, diagnosis, lab results, APACHE II/SOFA scores, and outcomes. Ammonia levels were monitored before and during SLED. Success was defined by ammonia reduction and clinical improvement.

The SLED protocol used a 300 mL/min dialysate flow, 100–200 mL/min blood flow, and ultrafiltration of 0–2500 mL/session for 6–8 hours daily. SLED was stopped when ammonia remained <145 µg/dL (85 µmol/L) twice, 12–24 hours apart, with neurological improvement.

Results: The mean age was 41 ± 14.5. A total of 9 patients survived (3 ALF and 6 ACLF) with an overall mortality rate of 55%. Low Hb, albumin and high SOFA scores were found to be poor prognostic markers.

Conclusion: Hyperammonia causing hepatic encephalopathy in liver failure carries a high mortality rate and requires prompt lowering of the ammonia level to prevent brain damage. SLED can be considered in lowering ammonia level. Large-scale studies are required to further assess efficacy of SLED in treating hyperammonia.

Keywords: Sustained low-efficiency dialysis (SLED); hyperammonia; Hepatic encephalopathy; liver failure.

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Introduction

Hepatic encephalopathy (HE) is a potentially reversible disease but carries a high mortality rate if not treated in a timely fashion. Patients with acute or acute-on-chronic liver failure (ACLF) may experience a progression in the clinical characteristics of hepatic encephalopathy from mild to severe[1]. The advancement of hepatic encephalopathy to grade 3 or 4 is characterized by impairment of consciousness.

A number of chemicals, including ammonia, are neurotoxic and reduce excitatory neurotransmission[2]. Ammonia can also pass across the blood-brain barrier, where astrocytic glutamine synthetase transforms ammonia and glutamate into glutamine, which raises cerebral volume through osmosis, resulting in neuronal dysfunction and cerebral edema, particularly in patients with no prior liver failure[3]. Of patients with hepatic encephalopathy, up to 80% had elevated serum ammonia levels. Furthermore, concurrent renal failure might result in further hyperammonemia because the kidneys eliminate 20% of body's ammonia. Even though blood level of ammonia does not have a defined threshold that is correlated with the presence of neurological symptoms[4], arterial ammonia levels <75 µmol/L[5] or <128 µg/dl (range = 6-47 µmol/L or 10-80 µg/dL) are

rarely linked to higher intracranial pressure (ICP), while ammonia levels > 85 µmol/L (144.75 µg/dl) carry a higher risk of complications. Similarly, there was a higher risk of cerebral edema and a worse survival probability for patients with chronic hyperammonemia of >122 µmol/L (207.7 µg/dl) for three days in a row[4]. On the other hand, persistent levels over 150 µmol/L (or 255.5 µg/dl) are highly linked to elevated intracranial pressure (ICP), brain herniation, and even death[4,6].

Reducing ammonia absorption from the intestinal lumen with the use of lactulose or rifaximin is the aim of the early management of hepatic encephalopathy. It's still unclear how extracorporeal dialysis affects cerebral edema and blood ammonia levels; however, it has been reported that the use of renal replacement therapy (RRT) significantly lowers blood ammonia levels, resulting in clinical improvement in patients with cerebral edema when used early[2].

Our objective was to evaluate the effectiveness of sustained low-efficiency dialysis (SLED) as a type of renal replacement therapy (RRT), to correct hyperammonia in patients with stage 3 or 4 of hepatic encephalopathy secondary to acute or acute-on-chronic liver disease, and to correlate it with clinical improvement.

Methods

A total of 20 patients admitted to the Pakistan Kidney and Liver Institute and Research Centre (PKLI-RC), Lahore, between May 1st, 2022 and November 30th, 2023 were enrolled in the study.

Inclusion criteria: All adult patients with symptomatic hyperammonia (ammonia level > 145 µg/dl or 85 µmol/L) and in grade 3 or 4 hepatic encephalopathy [1,7] secondary to either acute liver failure or due to acute-on-chronic liver failure were enrolled in the study and offered SLED based on the aim to treat strategy.

Exclusion criteria: Pediatric patients and patients with normal ammonia and/or without signs of hepatic encephalopathy were excluded from the study.

Data obtained include age, gender, diagnosis, pre-SLED laboratory results, the first 24 hours APACHE II and SOFA score, and finally outcome (survivor vs. non-survivor) were the variables examined. The ammonia level was measured prior to the first and subsequent SLED sessions as well as daily. A good reduction in ammonia levels and the improvement in clinical status are the main indicators of success versus mortality.

SLED Protocol: Our SLED protocol runs dialysate flow (Qd) at 300 ml/min and blood flow (Qb) between 100 and 200 mL/min for 6-8 hours daily. Ultrafiltration ranged from 0 to 2500 ml/session. We discontinue SLED once the plasma ammonia concentration is < 145 µg/dl (85 µmol/L) on two occasions, 12–24 hours apart, along with concurrent neurological improvement,[8] as levels below this rarely cause raised ICP[5].

The PKLI hospital's ethics committee (PKLI-IRB/AP/138) has granted ethical approval.

Statistical Analysis: While categorical variables are stated using frequencies and percentages, continuous variables are defined using the mean ± standard deviation (SD). A student t-test was used, assuming an unequal variance, and a p-value of <0.05 was considered statistically significant. Clinical improvement versus mortality are the main outcome measures. The IBM SPSS 20 statistical analysis program was used for the analysis.

Results

During the study period, a total of 20 patients admitted to the ICU with hyperammonia secondary to either acute liver failure (ALF: 6 patients) or acute-on-chronic liver failure (ACLF: 14 patients) were offered SLED. The number of SLED treatments per patient ranged from 1 to 7 (mean 2.2 ± 1.5).

Baseline characteristics of these patients are shown in Table 1. Mean age was 41 ± 14.5 years, predominantly males (90%), 85% were in septic shock, mostly with ACLF (13 out of 17 patients) and almost all were on mechanical ventilators (19 out of 20 patients) mainly to protect the airways due to the decreased level of consciousness from hepatic encephalopathy.

Prognostic markers are shown in Table 2, comparing the values between survivors and non-survivors. Although there is a decrease in serum urea, creatinine, and ammonia after SLED with an improvement in acidosis, statistically, none of them were significant in terms of prognosis. The mean APACHE II score was 29.5 ± 6.9 and the SOFA score was 14.6 ± 3.7 but statistically only SOFA was significant ($p<0.024$) while assessing mortality. Other significant prognostic markers in our study were albumin ($p< 0.037$) and serum Hb (p-value 0.048), while number of others did not show statistically significant values. Mortality was 50% in ALF patients (3 out of 6 patients) and 57% (8 out of 14) in ACLF patients but comparing the two groups did not show a statistical difference.

Prognostic markers for ALF and ACLF are compared in Table 3 to determine any difference between the two groups and found that raised INR is a bad prognostic indicator in ACLF patients but not true for ALF patients. Similarly, a high SOFA score was associated with a poor prognosis in ALF but was not statistically different in ACLF patients. Although ammonia was significantly reduced by SLED, it was not found to be a prognostic marker. No significant relationship was found between hepatic encephalopathy, hepato-renal syndrome, and septic shock when compared with the outcome.

Table 1: *Characteristics of patients treated with sustained low-efficiency dialysis (SLED).*

Variables	Values
Mean Age (years)	41 ± 14.5 [1]
Sex (male/female)	F = 2 (10%); M = 18 (90%)[2]
ALF	6 (30%)
ACLF	14 (70%)
• ACLF grade 3	13 (92.9%)
• ACLF grade 2	1 (7.1%)
Hepato-renal Syndrome (HRS)	11 (55%)
Hepatic Encephalopathy	
• Grade 3	5 (25%)
• Grade 4	15 (75%)
Cerebral edema on CT head	4 (20%)
Septic shock	17 (85%)
Number of SLED sessions	2.2 ± 1.5
Respiratory failure requiring Mechanical ventilation	19 (95%)
APACHE II Score	29.5 ± 6.9
SOFA Score	14.6 ± 3.7
Ammonia before SLED, µg/dl	368.8 ± 252.7
Ammonia after SLED, µg/dl	171.9 ± 146.7
Mortality (n = 11)	
• ALF	3 (50%)
• ACLF	8 (57.1%)

[1] $\bar{x}$ ± SD; all such values
[2] n = number of participant (%); all such values
M = Male; F = Female; ALF = Acute Liver Failure; CLD = Chronic liver disease; HRS = Hepato-renal Syndrome; APACHE = Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II Scoring; SOFA = Sequential Organ Failure Assessment Score.

Table 2: *Prognostic markers.*

Variables	Value	p-value
Mean Age (years)		
• Alive	40.7 ± 18.2 [1]	0.932
• Expired	41.3 ± 11.7	
Hb, g/L		
• Alive	11.2 ± 3.1	0.048
• Expired	8.6 ± 7.7	
Platelets, x 10^9/L		
• Alive	213.4 ± 119.1	0.267
• Expired	152.5 ± 116.7	
Glucose, mg/dl		
• Alive	111.1 ± 37.2	0.834
• Expired	115.6 ± 49.2	
Creatinine, µmol/L		
• Alive	3.02 ± 2.4	0.411
• Expired	3.95 ± 2.5	
Urea, mg/dl		
• Alive	78.9 ± 54.9	0.063
• Expired	140.4 ± 82.6	
Sodium, mEq/L		
• Alive	135.4 ± 4.25	0.058
• Expired	130.8 ± 5.92	
Bicarbonate, mmol/L		
• Alive	18.8 ± 11.6	0.139
• Expired	12.1 ± 6.1	
Albumin, g/dl		
• Alive	2.6 ± 0.6	0.037
• Expired	1.9 ± 0.7	
Total Bilirubin before SLED, mg/dl		
• Alive	7.1 ± 5.9	0.107
• Expired	14.7 ± 13.2	
INR, units		
• Alive	2.3 ± 1.2	0.168
• Expired	3.0 ± 1.0	
Lactate, mg/dl		
• Alive	10.1 ± 8.04	0.447
• Expired	13.07 ± 4.7	
pH		
• Alive	7.26 ± 0.16	0.392
• Expired	7.17 ± 0.2	
Ammonia, µg/dl		
• Before SLED	368.8 ± 252.7	0.003
• After SLED	171.9 ± 146.7	
APACHE II		
• Alive	27.7 ± 8.2	0.307
• Expired	31.1 ± 5.7	
SOFA score		
• Alive	12.2 ± 3.8	0.024
• Expired	17.0 ± 1.1	
CLIF-SOFA score in ACLF		
• Alive (n=6)	14.0 ± 1.4	0.038
• Expired (n=8)	15.75 ± 1.28	

[1] $\bar{x}$ ± SD; all such values

Table 3: *Comparison of prognostic markers between ALF and ACLF patients.*

Variables	ALF (6)		ACLF (14)	
	Value	p-value	Value	p-value
Mean Age (years)				
• Alive	18.0 ± 5.3 [1]	0.01	52 ± 7.3	0.054
• Expired	41.3 ± 14.8		41.3 ± 11.4	
Hb, g/L				
• Alive	13.9 ± 1.03	0.098	9.8 ± 2.8	0.349
• Expired	8.8 ± 3.2		8.5 ± 1.2	
Albumin, g/dl				
• Alive	3.04 ± 0.5	0.175	2.4 ± 0.6	0.139
• Expired	2.2 ± 0.7		1.8 ± 0.8	
INR, units				
• Alive	3.6 ± 0.5	0.026	1.6 ± 0.7	0.006
• Expired	2.4 ± 0.2		3.2 ± 1.1	
Ammonia before SLED, µg/dl				
• Alive	315.3 ± 72.4	0.264	507.9 ± 319.9	0.257
• Expired	152.8 ± 184.7		319.5 ± 214.2	
APACHE II				
• Alive	17.7 ± 5.9	0.098	32.7 ± 1.9	0.939
• Expired	27.3 ± 5.03		32.5 ± 5.6	
SOFA score				
• Alive	8.0 ± 1.4	0.032	14.3 ± 2.4	0.126
• Expired	17.5 ± 0.7		16.7 ± 1.3	
Ammonia, µg/dl				
Before SLED	234.1 ± 153.8	0.036	400.3 ± 283.5	0.013
After SLED	113.8 ± 107.4		184.6 ± 160.9	
Hepatic Encephalopathy, On admission				
• Grade 3	S = 2[2]; E = 0	0.2	S= 1; E= 2	0.615
• Grade 4	S = 1; E = 3		S = 5; E = 6	
HRS				
• No	S = 3 ; E = 3	N/A	S = 1; E = 2	0.615
• Yes	None		S = 5; E = 6	
Septic shock				
• No	S = 2; E = 0	0.2	S = 1 ; E = 0	0.429
• Yes	S = 1; E = 3		S = 5; E = 8	

[1] $\bar{x} \pm$ SD; all such values

[2] n = number of participants (%); all such values.

S = Survived; E = Expired; HRS = Hepato-renal Syndrome.

Discussion

Hyperammonia results in decreased excitatory neurotransmission[2,9], and astrocytes are the cerebral cells that are mostly impacted by hyperammonemia through glutamine pathway[3], leading to hepatic encephalopathy.

Although the greatest detrimental effects of hyperammonia on the brain are seen in both acute and chronic hyperammonemia, patients with acute hyperammonemia are more likely to experience cerebral edema and brain herniation[9].while those with chronic hyperammonemia secondary to chronic liver disease may experience encephalopathy and hyperammonemia-induced neurotoxicity[10]. This is because, in contrast to acute liver failure (ALF) the rise in serum ammonia in acute-on-chronic liver failure (ACLF) is slow and gradual, permitting compensatory mechanisms to enhance the metabolism of ammonia by other organs and lower the osmolarity[11].

Once neurological manifestations develop, hepatic encephalopathy (HE) is potentially a lethal condition that requires prompt intervention. Therefore, the goal is to treat acute hyperammonemia quickly to prevent brain damage[12]. As an initial step, lactulose and rifaximin are used to decrease the intestinal lumen's absorption of ammonia, which might be beneficial in patients with underlying chronic liver disease but lack supporting data in ALF; rather, lactulose may be linked to a higher incidence of ileus and intestinal dilatation[13].

Extracorporeal dialysis has been shown to reduce blood ammonia levels and hence ameliorate cerebral edema; nevertheless, its effectiveness has not been well-established, particularly in the adult population when compared to the juvenile group[14]. Although continuous renal replacement therapies (CRRT) are preferred to intermittent dialysis as they prevent the rebound effect but have a reduced rate of ammonia removal, however, by avoiding the significant hemodynamic and metabolic swings linked to intermittent dialysis, an elevated ICP can be prevented[15]. As the contribution of ammonia to plasma osmolality is negligible; therefore, even its rapid removal through intermittent dialysis, by means of ultrafiltration[16], is not associated with dialysis disequilibrium syndrome[17].

At our facility, we decided to start a sustained low efficiency dialysis (SLED) program because of it's elevated ammonia purification rate capability. We found hemoglobin (Hb), albumin, and SOFA scores as poor prognostic indicators, consistent with other research[18]. Despite the fact that dialysis significantly decreased ammonia levels (pre-SLED = 350.4 ± 259.4 µg/dl; post-SLED = 163.4 ± 147.9 µg/dl; p-value 0.003) the change did not reflect on outcome as a prognostic marker, which might be due to the smaller number of patients in our study and the big variation in values among patients. Nevertheless, it has been noted that the current ALF prognostic models rely on admission factors that might not be very accurate at predicting results[4].

Previous studies have shown high ammonia [5] and bilirubin [19]as poor prognostic markers in patients with

acute or acute-on-chronic liver failure, but in our patients, bilirubin was not found to be a significant factor. The risk categorization of ALF patients can be made dynamic with serial ammonia estimation, which can be more helpful when making treatment decisions. In our study, baseline ammonia was 368.8 ± 252.7 µg/dl which dropped significantly from SLED to 171.9 ± 146.7 µg/dl (p-value 0.003). This drop is present in each group of ALF and ACLF patients, reflecting mortality of 50% and 57.1%, respectively. Therefore, ammonia-lowering interventions should be strongly considered in both ALF and ACLF patients with symptomatic hyperammonemia. As compared to ACLF, patients with ALF having high INR did survive once they recovered from ALF itself.

Numerous studies have revealed that hepatic encephalopathy is a predictor of mortality. According to Xiong et al. [20] individuals with a higher grade of hepatic encephalopathy (grade 3 or 4) have poor outcome and Mainardi et al.[21], reported 94% mortality rate in these patients. We reported 50% mortality rate in ALF patients (without liver transplantation) with grade 3 and grade 4 hepatic encephalopathy in comparison to other studies that reported higher mortality[18,20,21].

With prevalence rates ranging from 20% to 35%, ACLF is far more common than ALF globally. The EASL-CLIF Consortium defines the worldwide reported death rate between 30% and 50%, which is closely correlated with the number of organ failures (Ofs) [22]. In patients with ACLF, CLIF-SOFA is a better predictor of mortality; using that, Perricone G et al. [22] suggested 4 sub-groups of ACLF as follows to assess mortality according to the number of organ failures (Ofs):

1. No ACLF: no OF or a single nonrenal OF without renal dysfunction and cerebral dysfunction.
2. ACLF grade 1 (ACLF-1): single renal failure and single nonrenal OF that is associated with renal dysfunction and/or cerebral dysfunction.
3. ACLF grade 2 (ACLF-2): two OFs of any combination.
4. ACLF grade 3 (ACLF-3): three or more OFs of any combination.

13 out of 14 of our ACLF patients were in ACLF grade 3, and 1 was in grade 2. This makes them a high mortality group, as the average 28-day mortality rates for ACLF grades 2 and 3 without liver transplantation (LT) were 31% and 74%[22]. Our ACLF (combined for group 2 and 3) patients' mortality was 57.1% which is less than reported by Perricone G [22].

Our overall mortality rate was high at 55% given the fact that our patients had high baseline APACHE II and SOFA scores with multi-organ failure, septic shock (85%) and mechanical ventilation (95%). However, the mortality for ALF and ACLF was 50% and 57.1% which is less than previous studies[18,20,21,22]. likely due to additional treatment from SLED to lower hyperammonia aggressively.

Therefore, we advocate that RRT should be taken into consideration when the patient exhibits severe encephalopathy and blood ammonia level exceeds the upper limit of normal by three times [23], especially before acute kidney injury (AKI) develops to prevent the hyperammonia from causing irreversible brain damage[12,24]. This approach was associated with increased transplant-free survival in acute liver failure cases [24].

Furthermore, in the situation of hemodynamic stability, although not yet practiced at our centre, a hybrid protocol consisting of intermittent haemodialysis followed by a continuous approach could be proposed to improve ammonia elimination and prevent rebound effects[14].

Limitations: Our limitation was the small number of patients in the study. Therefore, we suggest that in the future, a large-scale study should be considered on SLED's role in hyperammonia patients and to compare its usefulness with CRRT.

Conclusion

Reduction of hyperammonemia-related clinical symptoms is one of the main objectives of renal replacement therapy (RRT). We found significant reduction of hyperammonia using sustained low-efficiency dialysis (SLED). The longer a patient's hyperammonemia lingers, the greater the chance of potential mental impairment; therefore, we propose to initiate RRT as soon as possible when patient is found to have hyperammonia as a cause of an altered level of consciousness to prevent brain damage. Our limitation is the small patient population, which might have affected our outcome; therefore, larger studies are required to further delineate the role of RRT in hyperammonia from liver failure.

Ethical Approval: The IRB/EC approved this study via letter no.PKLI-IRB/AP/138 dated-31-7-2023.

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Authors' Contribution

MR: Conception
SY, AR: Design of the work
SY, HMI, AA: Data acquisition, analysis, or

interpretation
MR, SY, AK: Draft the work
AK, AA,AR: Review critically for important intellectual content
MR, SY, HMI, AK, AA, AR: Approve the version to be published
MR, SY, HMI, AK, AA, AR: Agree to be accountable for all aspects of the work

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