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Plasma Exchange in Liver Failure - Insights from a Tertiary Care Experience

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ABSTRACT

Liver failure, encompassing both acute liver failure (ALF) and acute-on-chronic liver failure (ACLF), constitutes a severe and life-threatening medical emergency. These conditions are characterized by rapid functional decline of the liver, frequently progressing to multi-organ dysfunction. Plasma exchange (PLEX) has emerged as a promising adjunctive therapeutic strategy, primarily due to its capacity to eliminate circulating toxins and inflammatory mediators. This paper explores the application of PLEX in patients diagnosed with ALF and ACLF, evaluating its impact on their biochemical profiles and overall prognosis.

The study cohort comprised eleven patients, with an average age of 41 years (ranging from 8 to 64 years); nine of these patients were male. Of the total, three patients presented with ALF, and eight with ACLF. Participants underwent an average of 2.9 PLEX cycles over an average hospitalization period of 12.3 days (ranging from 3 to 22 days). PLEX treatment resulted in a notable improvement in serum levels of bilirubin, INR, and creatinine across the patient group. Five patients (45%) achieved a favourable clinical outcome. Furthermore, patients demonstrating a favourable outcome exhibited a significant reduction in serum bilirubin and INR levels when compared to those with an unfavourable outcome

The findings suggest that PLEX may offer potential benefits for patients afflicted with ALF or ACLF. Further research, incorporating a larger dataset, is necessary to conclusively establish its efficacy in the treatment of liver failure.

Keywords: Acute liver failure, acute on chronic liver failure, plasma exchange

INTRODUCTION

Acute liver failure (ALF) and acute-on-chronic liver failure (ACLF) are severe conditions characterized by sudden and significant liver damage, leading to symptoms like jaundice, hepatic encephalopathy (HE), and coagulopathy (prolonged prothrombin time). ALF occurs in individuals without pre-existing chronic liver disease, while ACLF affects those who already have chronic liver disease.[1] Both conditions carry a high risk of short-term mortality and necessitate prompt and aggressive medical intervention. [2,3] Liver failure can be triggered by infectious or non-infectious causes. Aside from a few specific instances, there are no cause-specific treatments for liver failure. Management primarily focuses on preventing further liver injury, early identification and treatment of complications such as raised intracranial hypertension, sepsis, bleeding, and renal failure, and utilizing organ support devices

while awaiting liver function recovery.[4,5] Systemic inflammation plays a crucial role in the development of liver failure, contributing to immune dysfunction and organ failure, particularly renal failure, which is a leading cause of death in these patients. The massive liver cell death releases a surge of pro-inflammatory cytokines e.g., interleukin (IL)-6, IL-8 and damage-associated molecular patterns (DAMPs). Liver support devices have been explored to temporarily assist the liver's excretory functions and achieve partial detoxification. [6-8] Plasma exchange (PLEX) is a therapeutic procedure where a patient's plasma is replaced with an equivalent volume of fresh plasma from blood donors.[9] Donor plasma is preferred over synthetic colloids in acute liver failure because it helps correct clotting abnormalities and restores plasma proteins and volume. PLEX is classified as an ASFA (American Society for Apheresis) category III therapy for both ALF and ACLF, indicating its acceptance as an adjunctive treatment to improve biochemical markers and clinical outcomes. [9] The ASFA guidelines recommend high-volume plasma exchange Category I (8-12 litres or 15% of ideal body weight per session) for ALF. [9] However, due to considerations like patient tolerance and resource availability in certain settings, standard volumes (1-1.5 litres) may be used. PLEX supports liver function by removing harmful metabolic by-products and pro-inflammatory cytokines, while simultaneously replenishing procoagulant and anticoagulant proteins and factors normally synthesized by a healthy liver. Recent systematic reviews suggest that plasmapheresis has beneficial effects in patients with liver failure.[10] Experience with PLEX in liver failure patients in India is limited.[11-13] We present our initial experience with PLEX in liver failure patients treated at a tertiary care centre in Western India.

MATERIALS & METHODS

This retrospective analysis was conducted at a tertiary care centre in Western India, examining data collected from January 1, 2024, to December 31, 2024. The study included patients diagnosed with either acute liver failure (ALF) or acute-on-chronic liver failure (ACLF). Patients undergoing plasmapheresis (PLEX) for conditions other than liver failure were excluded. ALF was defined by the universal criteria of jaundice, coagulopathy, and hepatic encephalopathy in individuals with no history of liver disease. The diagnosis of ACLF required a combination of jaundice (serum bilirubin >5 mg/dL) and coagulopathy (either INR >1.5 or prothrombin activity < 40%), complicated within four weeks by clinical ascites and/or encephalopathy, in patients with known or undiagnosed chronic liver disease or cirrhosis[1]. Our primary objective was to assess the outcome at discharge, categorizing it as either favourable or unfavourable. A favourable outcome was defined as discharge in a hemodynamically stable state without hepatic encephalopathy. Conversely, patients who died or were discharged in a severely ill state were classified as having an unfavourable outcome. Prior, baseline measurements of serum bilirubin, serum creatinine, PT/INR, SGOT/SGPT, serum albumin, and electrolytes were obtained. During the PLEX procedure, essential patient parameters were monitored hourly. Each PLEX cycle, lasting approximately 2.5 to 4 hours, involved replacing 1 to 1.5 times the estimated plasma volume with fresh frozen plasma (FFP). PLEX was performed using a COMTEC machine (Fresenius Kabi India Pvt. Ltd., a subsidiary of Fresenius Kabi AG Germany) via a central venous catheter inserted into the internal jugular vein. Multiple PLEX cycles were administered at 48-hour intervals, as determined by the primary consulting team based on the patient's clinical condition. Plasma volume was calculated using established physiological variables, including sex,

height, weight, body muscle composition, and haematocrit [14]. A 1 to 1.5 plasma volume exchange is estimated to remove approximately 70% of intravascular substances [15]. After calculating the exchange volume, the patient's plasma was replaced with Fresh Frozen Plasma. The anticoagulant acid citrate dextrose was maintained at a 1:12 ratio with whole blood, and the blood flow rate was set between 30 and 50 mL/minute. Throughout the procedure, patients were closely monitored every hour for blood pressure, pulse, changes in appearance, and the development of symptoms such as light-headedness, nausea, paraesthesia, and overall status. To prevent citrate toxicity in patients with low calcium levels, 10 mL of calcium gluconate diluted in 100 mL of normal saline was administered intravenously at a slow infusion rate (1.83 mL/minute) over one hour[16]. If hypotension occurred, normal saline was infused, and the PLEX procedure was temporarily paused. All therapeutic plasma exchange (TPE) procedures were conducted in a designated area by blood centre technicians trained in TPE, under the supervision of a Blood Centre medical officer and the attending physician. Complications and adverse reactions were thoroughly assessed both during and after the procedure.

RESULT

A total of eleven patients were included in this study. Their baseline clinical characteristics and initial laboratory investigations are presented in Table 1. Participants underwent a mean of 3 (range: 1–6) cycles of plasma exchange (PLEX) during their hospital stay, which had a mean duration of 12 (range: 3–22) days. Significant improvements in relevant laboratory parameters were observed after PLEX, as detailed in Table 2. Serum bilirubin, INR, and serum creatinine levels significantly improved post-PLEX. Specifically, there was a 32.3% reduction in serum bilirubin, a 37.03% reduction in INR, and a 40% reduction in serum creatinine when comparing pre- and post-PLEX values. Further analysis, comparing patients with favourable versus unfavourable outcomes (Table 3), revealed notable differences. Patients achieving a favourable outcome demonstrated a 52% reduction in serum bilirubin, a 36% reduction in INR, and a 30% decrease in creatinine levels. In contrast, patients with unfavourable outcomes did not show a substantial reduction in these parameters. Overall, five patients (all 5 with ACLF) experienced a favourable outcome. Tragically, two patients passed away (1 with ALF and 1 with ACLF), and four patients (2 with ALF, 2 with ACLF) were discharged in a severely ill condition at their families' request. The number and frequency of PLEX procedures were tailored to the patient's clinical improvement, with some requiring long-term maintenance. The incidence of adverse reactions was 18% (2 cases), comprising hypotension (9%) and allergic reactions to plasma proteins (9%). Importantly, no mortality occurred during the PLEX procedures themselves. The mean hospital stay for patients with favourable outcomes was 11.8 (range: 7–15) days, while for those with unfavourable outcomes, it was 11.1 (range: 6–22) days. During their hospitalization, patients with favourable outcomes received a median of 2 (range: 1.5–2.0) PLEX cycles, compared to 1.5 (range: 1–2) cycles for those with unfavourable outcomes. Among the eleven patients, six developed hepatic encephalopathy (HE) during their hospital course, graded using the West Haven Criteria. The majority of these (3 patients) presented with Grade III HE, while one case each was observed for Grade I, Grade II, and Grade IV HE. Of these six patients with HE, four ultimately had an unfavorable outcome.

Table 1.- Patient characteristics and laboratory investigations before plasma exchange	
Patient Characteristics	**Values**
Age (years) (Range)	41 (8-64)
Male (%)	9 (81%)
Female (%)	2 (19%)
Diagnosis n (%)	
ALF	3 (27)
ACLF	8 (72)
Etiology of liver failure n (%)	
Hepatitis A with E virus	3 (27)
Hepatitis B virus	3 (27)
Alcohol	2 (18)
NASH	1 (9)
Not known	2 (18)
Laboratory investigations	**Mean (Range)**
Hemoglobin (g/dL)	9.8 (6.9-11.2)
Total white cell count (×1000/mm^3)	17.6 (6.9-96)
Platelet counts (×109/mm^3)	1.1 (0.8-1.5)
Total serum bilirubin (mg%)	23.2 (17.6-28.3)
Total serum protein (g/dL)	6.2 (5.6-6.9)
Serum albumin (g/dL)	3.1 (2.7-3.2)
Alanine aminotransferase (IU/L)	805 (66-4031)
Aspartate aminotransferase (IU/L)	914 (14-4774)
INR	2.7 (1.3-5.3)
Serum sodium (mEq/L)	135 (125-139)
Ammonia (mmol/L)	91.2 (55-124)
Serum creatinine (mg/dL)	1.2 (0.4-1.6)

Table 2- Comparison of laboratory parameters before and after plasma exchange			
Parameters	**PLEX- Mean (Range)**		
	Before	**After**	**p- value**
Serum bilirubin (mg/dL)	22 (3.24-60)	13.1 (3.21-47.6)	0.0004
INR	2.7 (1.39-5.31)	1.7 (1.37-3.50)	0.03
Serum creatinine (mg/dL)	1.0 (0.4-2.2)	0.6 (0.5-1.5)	0.05

Table 3- The effect of PLEX on laboratory parameters between those with favorable or unfavorable outcomes						
Parameters	**Favorable outcome- Mean (Range)**			**Unfavorable outcome- Mean (Range)**		
	Before PLEX	**After PLEX**	***P value***	**Before PLEX**	**After PLEX**	***P value***
Serum bilirubin (mg/dL)	21.0 (17.3-26.5)	10.7 (11.2-17.4)	0.0001	25.9 (19.3-29.6)	17.7 (13.0-22.2)	0.0001
INR	2.2 (1.8-3.1)	1.4 (1.3-2.0)	0.00001	3.4 (3.0-4.1)	2.7 (2.2-3.4)	0.0001
Creatinine	1.0 (0.6-2.2)	0.7 (0.4-1.2)	0.03	1.35 (0.8-1.9)	1.05 (0.6-1.5)	0.01
PLEX=Plasma exchange, INR=International normalized ratio.						

DISCUSSION

In this study, we performed PLEX on eleven patients diagnosed with either acute liver failure (ALF) or acute-on-chronic liver failure (ACLF). Approximately half of these participants experienced a favourable outcome, receiving a median of 2.9 (range: 1–6) cycles of PLEX during their median hospital stay of 12.3 (range: 3–22) days. Patients with favourable outcomes exhibited significant improvements in serum bilirubin and INR compared to those with unfavourable outcomes. The severely altered biochemical environment in liver failure patients is characterized by accumulation of gut-derived toxins, a surge of inflammatory cytokines released from damaged hepatocytes and immune cells, the

production of ammonia by intestinal bacteria, and a critical reduction in both pro- and anti-coagulation factors synthesized by the liver [17]. Given the high mortality risk associated with liver failure and the lack of a definitive cure, PLEX has emerged as a crucial management strategy. It offers detoxification by reducing the concentration of these accumulated toxins, buying valuable time for either spontaneous liver regeneration and functional recovery or for a liver transplant to be performed. This treatment provides several benefits, including the elimination of inflammatory cytokines, the restoration of vital coagulation factors, and the removal of circulating toxins and damage-associated molecular patterns (DAMPs). Despite the research on PLEX in ALF and ACLF, there remains a lack of consensus on several critical procedural aspects, including the optimal volume of plasma to be exchanged in each cycle, the total number of cycles required, and the ideal frequency and intervals between successive PLEX treatments [10]. The current evidence supporting the use of PLEX in liver failure patients primarily stems from a limited number of cases reports [12, 18] and a single prior study conducted in India [11]. This particular Indian study focused exclusively on ALF cases linked to yellow phosphorus poisoning, a common aetiology in certain southern regions of the country. Notably, that study reported that PLEX enabled 44% of patients to avoid the need for a liver transplant. Internationally, a randomized controlled trial by Larsen et al. involving 182 ALF patients demonstrated that high-volume PLEX led to improved outcomes, specifically by enhancing liver transplant-free survival rates[19]. In contrast to the aforementioned studies, our data included both ALF and ACLF patients, reflecting a broader spectrum of aetiologies prevalent in our region of India. Our findings further support the utility of PLEX, demonstrating significant improvements in key clinical parameters associated with liver failure outcomes, including INR, creatinine levels, and serum bilirubin. Crucially, the magnitude of improvement in these parameters was notably greater in patients who achieved a favourable outcome compared to those with an unfavourable prognosis. Consistent with other observations, our study also indicated that patients presenting with Grade III and IV Hepatic Encephalopathy had a poorer prognosis. Our study, however, is not without limitations. These include a relatively small sample size and a heterogeneous study population, which may limit the generalizability of our findings. Looking ahead, future studies with larger sample sizes are warranted to precisely identify biochemical parameters that could serve as reliable predictors of outcome following PLEX. Such insights would be invaluable in guiding clinical decision-making, helping clinicians determine whether to continue PLEX or proceed with liver transplantation in patients with liver failure.

CONCLUSION

Our limited experience with plasma exchange in patients with liver failure suggests that it is a reasonably effective therapeutic intervention. However, to definitively ascertain its role and establish its routine use in the management of liver failure, further data from larger, multicentric studies are imperative.

Limitations

This study has several limitations that warrant consideration. Firstly, the small sample size restricts the generalizability of our findings to a broader patient population. Conclusive statements regarding the widespread applicability of PLEX would require data derived from a substantially larger cohort. Secondly, the absence of a control group makes it challenging to definitively attribute the observed clinical and biochemical improvements solely to PLEX, as concurrent treatments may have also contributed to the patient outcomes. Finally, the lack of long-term follow-up data

prevents us from assessing the sustained benefits and long-term impact of PLEX on patient prognosis. Future research should address these limitations to provide more robust evidence regarding the efficacy and optimal utilization of PLEX in liver failure.

Declaration by Authors

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