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A preliminary experience of plasma exchange in liver failure

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Abstract:

INTRODUCTION: Plasma exchange (PLEX) is one of the experimental modalities of treatment for liver failure. We report our experience of PLEX in patients with acute-(ALF) or acute-on-chronic (ACLF) liver failure.

METHODS: Hemodynamically stable adult patients with ALF or ACLF, encephalopathy, model for end-stage liver disease (MELD) score ≥ 15, and clinical worsening/no improvement after 72-h of inpatient care were included. PLEX cycles repeated every 48 h, each of 2.5–4.0 h duration with 1–1.5 times of estimated plasma volume, were given. PLEX cycle was repeated till either of the end-points were achieved (i) MELD < 20 for 48 h or reaches below the baseline, whichever is lower, (ii) completed three PLEX cycles, (iii) hemodynamic instability, (iv) or outcome achieved. Outcome of interest was categorized as favorable (discharged in stable condition) or unfavorable (death or discharge in moribund condition). Data are expressed as median (interquartile range).

RESULTS: Sixteen patients (age 35 [27–48] years; male 8; ALF 5, ACLF 11; MELD 33 [27–37]; CLIF-SOFA 10 [8.5–12]) were included. Participants received 2 (1-3) cycles of PLEX during 13 (11–25) days of hospitalization. Overall, serum bilirubin, INR, creatinine, MELD, and CLIF-SOFA scores were significantly improved after PLEX. Five patients (5/16, 31%) had complete resolution of HE. Eight patients (50%) had a favorable outcome. Those with favorable outcome had significant improvement in serum bilirubin, INR, and CLIF-SOFA scores as compared to those with unfavorable outcome.

CONCLUSION: PLEX may be effective in patients with ALF or ACLF. More data are needed to establish its role in the management of liver failure.

Keywords:

Acute liver failure, acute on chronic liver failure, liver assistive device, plasmapheresis

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Introduction

Sudden and massive liver injury results in liver failure characterized by jaundice, hepatic encephalopathy (HE), and coagulopathy or prolonged prothrombin time (PT). Liver failure may occur in patients with or without preexisting chronic liver disease (CLD) and is known as acute-on-chronic liver failure (ACLF) and acute liver failure (ALF), respectively.[1] Both, ALF and ACLF, are at high-risk for death in short period of time and need aggressive management.[2,3]

Infective or noninfective aetiologies could precipitate liver failure. Barring a few of them, we do not have a cause-specific treatment in liver failure. Management of liver failure is primarily focused on avoiding the further liver injury, early identification, and management of its complication such as raised intracranial hypertension, sepsis, bleeding, renal failure, and use of organ support devices while waiting for spontaneous recovery of liver functions.[4,5]

Systemic inflammation plays a key role in the pathogenesis of liver failure associated

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immune paralysis and organ failure such as renal failure, which are the most common cause for death in such patients. The sudden and massive necrotic injury releases a storm of pro-inflammatory cytokines such as interleukin (IL)-6, IL-1 β, IL-8, and damage associated molecular patterns (DAMPs) from necrotic hepatocytes and several other injured cells. Several experimental liver support devices have been used which temporarily circumvent the excretory functions of liver and achieve, at least, partial detoxification.[6-8]

Plasma exchange (PLEX) is an experimental therapy in which the patient's plasma is replaced with equal volume of freshly collected blood donors' plasma.[9] The PLEX supports the liver by removing the harmful metabolic products, pro-inflammatory cytokines and replacing the procoagulant and anticoagulant proteins and factors synthesized by normal liver. A recent systematic review has suggested the beneficial effect of plasmapheresis in patients with liver failure.[10] There is a very limited experience from India on its use in liver failure patients.[11-13] Here, we report our small experience with PLEX in liver failure patients managed in a tertiary care center in the northern part of India.

Methods

This prospective study was conducted in Department of Internal Medicine, King George's Medical University (KGMU), Lucknow, India. The participants were enrolled from August 2018 to July 2019. Adults (>18 years) patients with ALF or ACLF, for who liver transplantation was not an option due to any reason, were screened for selection criteria. We included hemodynamically stable adults with HE and model for end-stage liver disease (MELD) score ≥ 15 who had shown either no improvement or deterioration of clinical condition after 72 h of standard of care as inpatient. Clinical deterioration was defined as the presence of either worsening of HE, MELD score more than ≥ 20, or increase in serum creatinine by either 50% or ≥ 0.3 mg% from the level at admission.[14] The patients with preexisting chronic kidney disease, brain death, ongoing or prior malignancy, coronary artery disease, renal failure, or organ transplant recipients were excluded.

ALF was diagnosed with a universal criterion of jaundice, coagulopathy (INR ≥ 1.5), and HE in a person without preexisting liver disease. The ACLF was defined with a combination of jaundice (serum bilirubin ≥ 5 mg/dl) and coagulopathy (INR ≥ 1.5 or prothrombin activity < 40%) complicated within 4 weeks by clinical ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed CLD/cirrhosis.[1] All those included in study were managed with standard of care recommended for the management of ALF or ACLF.[5,15]

Our primary objective was favorable or unfavorable outcome at the time of discharge. Favorable outcome was defined as discharge in hemodynamically stable condition without HE. Those who died or were discharged in moribund condition were counted to have unfavorable outcome. Secondary outcomes were changes in HE grades, PT prolongation, and liver disease severity score as assessed with MELD and CLIF-SOFA scores.[16]

Serum creatinine and electrolytes were checked before PLEX. Vital parameters of the participants were hourly monitored during the process of PLEX. In each PLEX cycle, which continued for 2.5 to 4 h, approximately 1–1.5 times of estimated plasma volume was exchanged with fresh plasma. PLEX was performed with COMTEC (manufactured by Fresenius Kabi India Pvt. Ltd., a subsidiary of Fresenius Kabi AG Germany) machine through central venous catheter placed in internal jugular vein. Following each PLEX cycle, MELD score was calculated at an interval of 24 h. Repeated cycles of PLEX were given at an interval of 48 h till either of the end-point was achieved (i) MELD stayed below 20 for 48 h or below the baseline MELD, whichever was lower (ii) three cycles of PLEX were completed (iii) unstable hemodynamic condition (iv) or the patient had achieved primary outcome.

Categorical and numerical data were expressed as proportion and median (interquartile range). MannWhitney *U*-test and Wilcoxon signed-rank test was used for comparison of unpaired and paired numerical data, respectively.

Study was approved by KGMU Ethics Committee and the participants were enrolled after obtaining written informed consent from the spouse or legal guardian, as applicable.

Results

Sixteen patients were included. Baseline clinical characteristics, laboratory investigations, and liver disease severity scores of the study participants are summarized in Table 1. The participants received 2 (1–3) cycles of PLEX during their hospital stay of 13 (11–25) days. The grade of encephalopathy, relevant laboratory parameters, and liver disease severity scores before and after PLEX are compared in Table 2. The serum bilirubin, INR, serum creatine, and liver disease severity score were significantly improved after PLEX. Although HE grade was not significantly changed with PLEX, five patients (5/16, 31%) had complete resolution of HE. Overall, eight patients (6 ACLF, 2 ALF) had a favorable outcome, six expired (3 ALF, 3 ACLF), and two ACLF patients were discharged in moribund condition on request of the family members.

Table 1: Clinical characteristics and laboratory investigations of the participants before plasma exchange

Characteristics	Values
Age (years)	35 (27-48)
Male (%)	8 (50)
Diagnosis	
ALF	5 (31)
ACLF	11 (69)
Etiology of liver failure	
Hepatitis B virus	6 (38)
Hepatitis E virus	3 (19)
Alcohol	1 (6)
Wilson's disease	1 (6)
Not known	5 (31)
Laboratory investigations	
Hemoglobin (g/dL)	10.7 (9.5-11.3)
Total white cell count (×1000/mm^3)	10.6 (6.3-14.6)
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)	295 (82-427)
Aspartate aminotransferase (IU/L)	424 (117-556)
INR	3.1 (2.0-3.6)
Serum sodium (mEq/L)	136 (134-143)
Serum potassium (mEq/L)	3.8 (3.4-4.4)
Serum creatinine (mg/dL)	1.0 (0.6-1.3)
Severity of HE	
Grade 1	1 (6)
Grade 2	7 (44)
Grade 3	5 (31)
Grade 4	3 (19)
Disease severity scores	
MELD score	33 (27-37)
CLIF-SOFA	10 (8.5-12)

Numbers in parentheses are either percentage or IQR. INR=International normalized ratio, IQR=Interquartile range, MELD=Model for end-stage liver disease, ALF=Acute liver failure, ACLF=Acute on chronic liver failure CLIF=Chronic liver failure, SOFA=Sequential organ failure assessment score, HE=Hepatic encephalopathy

Table 2: Comparison of clinical and laboratory parameters before and after plasma exchange

Parameters	PLEX		*P*
	Before	After	
Serum bilirubin (mg/dL)	23.2 (17.6-28.3)	15.7 (13-19.7)	<0.01
INR	3.1 (2.0-3.6)	2.1 (1.4-2.7)	<0.01
Serum creatinine (mg/dL)	1.0 (0.6-1.3)	0.6 (0.5-0.9)	0.01
Severity of HE			
Grade 0	0	5 (31)	0.12
Grade 1	1 (6)	4 (25)	
Grade 2	7 (44)	2 (12.5)	
Grade 3	5 (31)	3 (19)	
Grade 4	3 (19)	2 (12.5)	
Disease severity scores			
MELD score	33 (27-37)	25 (21.5-29)	<0.01
CLIF-SOFA	10 (8.5-12)	8 (6-12)	0.04

Numbers in parentheses are either percentage or IQR, Wilcoxon-Signed Rank test was used for comparison. PLEX=Plasma exchange, INR=International normalized ratio, IQR=Interquartile range, MELD=Model for end-stage liver disease, CLIF=Chronic liver failure, SOFA=Sequential organ failure assessment score, HE=Hepatic encephalopathy

The effect of PLEX on HE grades, laboratory parameters, and the liver disease severity scores between those with favorable or unfavorable outcomes are compared in Table 3. The participants with favorable outcome had significant improvement in serum bilirubin, INR, and CLIF-SOFA scores as compared to those who had an unfavorable outcome. The MELD had improved significantly in both the groups. The hospital stay of those with favorable and unfavorable outcome was 18.5 (12.5–27.5) days and 12 (8–18) days, respectively; during the hospital stay those with favorable and unfavorable outcome had received 2 (1.5–2.0) and 1.5 (1–2) cycles of PLEX, respectively.

Discussion

PLEX was done in sixteen patients with ALF or ACLF. Half of the participants had favorable outcome after receiving 2 (1–3) cycles of PLEX during their hospital stay of 13 (11–25) days. Serum bilirubin, INR, serum creatine, and liver disease severity score were significantly improved after PLEX. The participants with favorable outcome had significantly higher improvement in serum bilirubin, INR, and CLIF-SOFA scores as compared to those with unfavorable outcome.

The biochemical milieu of the patient in liver failure is markedly disturbed due to accumulation of gut-derived toxins, inflammatory cytokines produced by injured hepatocytes and inflammatory cells, ammonia derived from luminal bacteria, and reduction in concentration of pro-and anti-coagulation factors produced by hepatocytes.[17] Liver failure patients are at high risk of death. There is no specific treatment for liver failure. Several artificial devices, such as Molecular Adsorbent Recirculating System or MARS, have been used in its management which can replace the functions of the liver for a period of time, till either the native liver regenerates and regains its functional capabilities or liver transplantation is done.

PLEX is one of those methods in which the patient's plasma is replaced with donor's plasma. In high volume PLEX, the plasma volume used in exchange is at least equal to the estimated plasma volume in a patient.[18] PLEX may bring beneficial effects by multitude of effects such as removal of inflammatory cytokines, replenishment of coagulation factors, and removal of circulating toxins and removal of DAMPs.

In our experience of PLEX in liver failure, the survival without liver transplantation was similar to that seen in a recent systematic review of 44 studies.[10] Although we have multiple studies on the use of PLEX in ALF and

Table 3: Effect of plasma exchange in those with favorable or unfavorable outcomes

Parameters	Favorable outcome			Unfavorable outcome		
	Before PLEX	After PLEX	*P*	Before PLEX	After PLEX	*P*
Serum bilirubin (mg/dL)	21.0 (17.3-26.5)	15.7 (11.2-17.4)	0.01	25.9 (19.3-29.6)	17.7 (13.0-22.2)	0.05
INR	2.2 (1.8-3.1)	1.4 (1.3-2.0)	0.01	3.4 (3.0-4.1)	2.7 (2.2-3.4)	0.05
Creatinine	0.9 (0.7-1.1)	0.6 (0.5-0.8)	0.08	1.0 (0.6-2.0)	0.7 (0.6-1.0)	0.05
HE grades 0/1/2/3/4	0/0/6/2/0	4/4/0/0/0	1.00	0/1/1/3/3	1/0/2/3/2	0.12
MELD score	27 (25.5-33)	21.5 (20-25)	0.01	34.5 (33-37)	29 (24.5-31.5)	0.02
CLIF-SOFA score	8.5 (7.5-10)	6 (5-7)	0.01	12 (10.5-13.5)	12 (10-14)	0.94

Numbers in parentheses are either percentage or IQR, Mann-Whitney *U* test was used for comparison. PLEX=Plasma exchange, INR=International normalized ratio, IQR=Interquartile range, HE=Hepatic encephalopathy, MELD=Model for end-stage liver disease, CLIF=Chronic liver failure, SOFA=Sequential organ failure assessment score

ACLF, all those studies are not of good quality and till today, we have no consensus about the volume of plasma used in each cycle, total number PLEX cycles, frequency and interval between the two PLEX cycle.[10]

The data on use of PLEX in patients with liver failure are limited to a few case reports[12,19] and a single study.[11] The study was exclusively done in patients with yellow-phosphorus related ALF[11] which is commonly seen in Southern states of India. This study found that, with PLEX, the need for liver transplant was avoided in 44% of patients. Internationally, a randomized control trial on 182 patients with ALF showed that high volume PLEX resulted in better outcomes by increasing liver transplant-free survival.[20] Our data, in contrast to previous study, included both, ALF and ACLF patients which were related to a mix of aetiologies commonly seen in our country. In addition, we also found that with PLEX, various parameters which determine the outcome of a patient with liver failure, such as INR, creatinine, serum bilirubin, disease severity score, were improved with PLEX. Although five of the patients became free of HE, it could not reach the level of significance which could be because of small sample size. The improvement in these parameters was significantly more in those with favorable outcome than those with unfavorable outcomes.

Our data had a few limitations such as small sample size and heterogenous study population. We have also not measured the serum levels of inflammatory markers such as cytokines and interleukins which could identify the PLEX mediated subclinical changes in internal milieu of the patient.

In future, study with large sample size is needed to identify the biochemical parameters which could serve as a predictor for outcome following PLEX which may help in decision making in favor of continued PLEX or liver transplantation in patients with liver failure.

Conclusion

In conclusion, in our small experience of PLEX in patients with liver failure, we found it reasonably effective. But more data, from larger multicentric studies are needed before drawing a conclusion about its regular use in patients with liver failure.

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Conflicts of interest

There are no conflicts of interest.

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