CASE SERIES

Role of therapeutic plasmapheresis in acute liver failure in paediatric patients: A case series

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Abstract

Paediatric acute liver failure (PALF) is a rare yet severe condition that is associated with high mortality. Apart from liver transplant, no specific therapy exists, particularly in developing countries. Evidence suggests that removal of damage-associated molecular patterns, cytokines, toxins, and other metabolites that accumulate due to impaired liver function can enhance natural recovery. Plasmapheresis can be used to remove these products; however, there is limited evidence to support this approach. This case series discusses three critically ill patients with acute liver failure who underwent plasmapheresis. The patients included a seven-year-old boy (Case 1), a 17-year-old boy (Case 2), and a 16-month-old boy (Case 3). Two patients showed significant improvement in bilirubin level, coagulation profile, inotropes requirement, and Glasgow coma scale score. Unfortunately, one patient with PALF, complicated with multi-organ dysfunction, died due to refractory shock on the fourth day of hospitalisation. Our findings illustrate that early use of therapeutic plasmapheresis in PALF can lead to improvement in clinical outcome. It may serve as a bridging therapy for liver transplant and for the spontaneous regeneration of the patient's liver.

Keywords: Acute liver failure, Plasmapheresis, Plasma exchange, Hepatitis.

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Introduction

Paediatric acute liver failure (PALF) is a nearly fatal condition if liver transplant (LT) is not done. In Pakistan, the most common causes of acute liver failure are viral hepatitis A, followed by seronegative hepatitis, sepsis, and malignancy.[1] However, it is worth noting that in many cases, the aetiology of acute liver failure remains unknown. A study by Larson-Nath and Vitola highlights the complexity of paediatric acute liver failure and emphasises that more than 50% of cases have an unknown aetiology.[2] Pathologically, hepatocyte damage leads to release of damage-associated molecular patterns (DAMPs), which causes the activation of immune cells and initiation of an inflammatory response, with the release of cytokines such as tumour necrosis factor (TNF)-alpha, Interleukin (IL)-1 and IL-6.[3] These cytokines and toll-like receptor activate macrophage causing tissue damage and further cytokine production.[4] The use of N-acetylcysteine (NAC) in a patient with fulminant liver failure secondary to viral hepatitis has been controversial.[5] Extracorporeal liver support system (ELSS) provides support for acute liver failure, and it can act as a bridge to either spontaneous recovery or successful liver transplantation. Plasma exchange (PE) is a well-studied modality among all ELSS.[6] Plasma exchange (PE) is effective in modulating the pro-inflammatory response by removing DAMPs[7] Currently, very limited data is available for the use of PE in paediatric acute liver failure. The decision to use PE is made on case-by-case basis. The aim of this study was to share our experience of PE in PALF. Here, we report a case series of paediatric patients with acute liver failure who underwent plasmapheresis.

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Case 1

A seven-year-old boy of Asian descent, a known case of type 1 diabetes, presented to Aga Khan University Hospital, Karachi, in January 2023, with fever for one week, jaundice for four days, brownish-red urine and altered consciousness for two days. No prior history of liver disease and relevant family medical history were reported. Examination showed jaundice, pallor, and drowsiness with Glasgow coma scale[8] (GCS) score of 9/15. The rest of the systemic examination was unremarkable. Laboratory findings were suggestive of multi-organ dysfunction syndrome with elevated bilirubin, liver enzymes, and coagulation profile (Table1). Further extended investigations revealed a positive viral serology of Hepatitis A, antinuclear antibody (ANA) titre of 1/80, normal anti double stranded DNA, negative dengue IgM antibody, negative ICT malaria antigen, blood urea nitrogen (BUN) 30, creatinine 1.8mg/dl, and C-reactive protein (CRP) 12.5 mg/dl. Coombs test was also positive. The Paediatric End-stage Liver disease (PELD) score[9] at the time of admission was 36.4. The patient was admitted to the paediatric intensive care unit, intubated due to

Table-1 : Case 1 patient's clinical parameters before and after Therapeutic Plasma exchange (TPE).

Diagnosis: Viral Hepatitis (HepA IgM positive) and Autoimmune Phenomenon (ANA: positive and ADNA: Negative).

Clinical parameter	Before TPE	After five sessions of TPE	Follow up visit
Total bilirubin (mg/dl)	51.5 (0.1-1.2)	12.4 (0.1-1.2)	7.9 (0.1-1.2)
Direct bilirubin (mg/dl)	41.5 (0-0.2)	9.2 (0-0.2)	6.4 (0-0.2)
Alanine aminotransferase (IU/L)	3830 (<45)	172 (<45)	98 (<45)
PELD score	54.6	30.4	N/A
PT (seconds)	78.7 (9.3-12.8)	13.7 (9.3-12.8)	11.5 (9.3-12.8)
INR (ratio)	8.2 (0.9-1.2)	1.3 (0.9-1.2)	1.1 (0.9-1.2)
Ammonia (ug/dl)	8 (<68)	-	-
GCS	9	15	15
VIS	08	03	0

PELD: Paediatric end stage liver disease, PT: Prothrombin time, INR: International normalized ratio, GCS: Glasgow coma scale, VIS: Vasoactive inotropic score, N/A: Not applicable.

deteriorating GCS on the first day of admission, and continued on mechanical ventilation. Supportive measures, including inotropes (vasoactive Inotropes Score VIS=06), intravenous fluids, neuroprotective measures, and N-acetylcysteine were initiated. A double lumen central venous catheter was passed into the internal jugular vein and Continuous Renal Replacement Therapy (CRRT) was started at 18 hours of presentation and continued for seven days. Plasmapheresis began at 19 hours of presentation and was conducted daily with each session lasting for two hours. During each session 1.5 times of the patient's plasma volume was exchanged with fresh frozen plasma as replacement fluid, and a total of five sessions were performed. After five sessions, significant improvements were observed in the liver profile, coagulation profile, and hepatic encephalopathy (Table 1). The PELD score and Vasoactive Inotropic Score (VIS)[10] also reduced significantly. No complications such as hypotension, hypocalcaemia, metabolic alkalosis, or haematoma/ bleeding at the catheter site were observed during plasmapheresis procedure. The patient remained stable with GCS of 10/10. Gas exchange was adequate with minimal ventilator parameters. He was extubated on the sixth day of hospitalisation, and diabetic medications were optimised. Inotropes were discontinued. He was discharged on the 14th day of hospitalisation. The patient returned to our clinic three weeks after discharge for follow-up appointment, where an assessment revealed improved jaundice and overall health as compared to the previous visit (Table 1).

Case 2

A 17-year-old boy of Asian descent presented to Aga Khan University Hospital, Karachi, in January 2023, with a history of fever for three days, vomiting, epigastric pain, and an altered level of consciousness since evening. No prior history of liver disease and relevant family medical history were reported. Examination showed jaundice, with GCS of 8/15; the rest of the systemic examination was unremarkable. Laboratory findings were suggestive of multi-organ dysfunction syndrome with elevated bilirubin level, liver enzymes, and coagulation profile (Table 2). Further investigations revealed positive viral serology of Hepatitis A, ANA titre 1/160, and lupus antibody with low C3 and C4, BUN 35, creatinine 3.3 mg/dl, CRP 7.6 mg/dl. Ceruloplasmin level, IgG and LKM-1 antibodies, ICT malaria antigen, Anti double stranded DNA were negative. Model for end stage liver disease (MELD) score[11] at the time of admission was 37. The patient was admitted to the paediatric intensive care unit, intubated due to low GCS, and continued on mechanical ventilation. Supportive measures, including inotropes (VIS=06), intravenous fluids, and neuroprotective measures were initiated. A double lumen central venous catheter was passed into the internal jugular vein and CRRT was started at 19 hours of presentation and continued for three days. Plasmapheresis began at 39 hours of presentation and was conducted daily for two hours per session. During each session, add 1.5 times plasma was exchanged with half fresh-frozen plasma and half normal saline, and a total of three sessions were performed. No complications such as hypotension, hypocalcaemia, metabolic alkalosis, or haematoma/ bleeding at the catheter site were observed during TPE procedure. During the hospital stay, he went into refractory shock and his inotropic requirements significantly increased. Additionally, his liver and coagulation profile deteriorated further (Table 2). Unfortunately, the patient expired on the fourth day of hospitalisation due to refractory shock with multi-organ dysfunction, and acute fulminant liver failure with coagulopathy.

Table-2 : Case 2 patient's clinical parameters before and after Therapeutic Plasma exchange (TPE).

Diagnosis: Viral Hepatitis (HepA IgM positive) and Autoimmune Phenomenon (ANA: positive, C3: 0.06gm/L, C4: 0.06gm/L and ADNA: Negative).

Clinical parameter	Before TPE	After three sessions of TPE
Total bilirubin (mg/dl)	3.9 (0.9-1.2)	4.6 (0.9-1.2)
Direct bilirubin (mg/dl)	2.9 (0-0.2)	3.6 (0-0.2)
Alanine aminotransferase (IU/L)	7367 (<45)	978 (<45)
MELD score	37	19.6
PT (seconds)	35 (9.3-12.8)	30 (9.3-12.8)
INR (ratio)	3.5 (0.9-1.2)	3.0 (0.9-1.2)
Ammonia (ug/dl)	249 (<68)	118 (<68)
GCS	08	N/A
VIS	06	100

MELD: Model end stage liver disease, PT: Prothrombin time, INR: International normalized ratio, GCS: Glasgow coma scale, VIS: Vasoactive inotropic score, N/A: Not applicable.

Case 3

A 16-month-old Asian boy presented to Aga Khan University Hospital, Karachi, in March 2023, with fever for one week, three days of respiratory distress, and altered consciousness for one day. No prior history of liver disease and relevant family medical history were reported. On examination, he was drowsy with GCS of 11/15 with no apparent jaundice, pallor, and oedema, and unremarkable systemic findings. Laboratory findings revealed elevated total bilirubin, liver enzymes, and coagulation profile. Plasma amino acid findings were suggestive of deficiency of cystathionine beta synthase. Further investigations showed BUN 17, creatinine 0.9 mg/dl, CRP 0.23 mg/dl, a negative ICT malaria antigen, viral serology for hepatitis A, hepatitis E, and normal urine toxicology. PELD score at the time of admission was 26.3. The patient was admitted to the paediatric intensive care unit, intubated due to low GCS and continued on mechanical ventilation. Supportive measures, including intravenous fluids, inotropes (VIS=08), antibiotics, neuroprotective measures, and N-acetylcysteine were initiated. A double-lumen central venous catheter was passed into the internal jugular vein. Plasmapheresis began at 10 hours of presentation, and the patient underwent a daily sessions of plasmapheresis of two hours each. During each session, twice the volume of the patient's plasma volume was exchanged with fresh frozen plasma and albumin as replacement fluid, and a total of three sessions were performed. After three sessions of PE, the liver profile, coagulation profile, and hepatic encephalopathy had significantly improved (Table 3). The PELD score and VIS score had also reduced significantly. During the second session of PE, the patient developed hypotension and hypocalcaemia which were managed by increasing inotropes and administering IV calcium chloride. No other complications were observed during TPE procedure. The patient remained stable with GCS of 10/10, with adequate gas exchange on minimum ventilator parameters, and was extubated and discharged on the seventh day of hospitalisation. Follow-up assessment after two weeks revealed that his jaundice and health had improved since the previous visit (Table 3), and he was referred to a metabolic specialist and geneticist for further evaluation of the disease but sample for genetic workup could not be processed due to financial reasons.

Table-3 : Case 3 patient's clinical parameters before and after Therapeutic Plasma exchange (TPE).

Diagnosis: Suspected metabolic disorder (Plasma amino acid showed marked elevation of methionine and decrease in cysteine)

Clinical parameter	Before TPE	After three sessions of TPE	Follow up visit
Total bilirubin (mg/dl)	3.1 (0.9-1.2)	2.4 (0.9-1.2)	0.7 (0.9-1.2)
Direct bilirubin(mg/dl)	2.8 (0-0.2)	1.6 (0-0.2)	0.4 (0-0.2)
Alanine aminotransferase (IU/L)	6661 (<45)	333 (<45)	79 (<45)
PELD score	26.3	7.5	N/A
PT (seconds)	36.0 (9.3-12.8)	15.3 (9.3-12.8)	9.8 (9.3-12.8)
INR (ratio)	3.7 (0.9-1.2)	1.5 (0.9-1.2)	0.9 (0.9-1.2)
Ammonia (ug/dl)	235 (<68)	103 (<68)	-
GCS	11	15	15
VIS	08	0	0

PELD: Paediatric end stage liver disease, PT: Prothrombin time, INR: International normalised ratio, GCS: Glasgow coma scale, VIS: Vasoactive inotropic score, N/A: Not applicable.

Discussions

The most common aetiology of acute liver failure in infants is metabolic disorder followed by sepsis.[12] In the case of ALF, extracorporeal liver support systems play a crucial role in removing albumin-bound or water soluble substances from the blood through various methods, which include albumin dialysis, plasma separation, plasma exchange, or a combination of these techniques.[13] The Paediatric End-stage Liver Disease (PELD) Score serves as a valuable tool in assessing the severity of liver disease and predicting the likelihood of survival for patients awaiting liver transplantation. The PELD score incorporates laboratory values such as bilirubin, INR, albumin, and growth failure, providing a numerical representation of the patient's disease severity. Higher PELD scores indicate a greater urgency for liver transplantation and are associated with an increased risk of mortality while on the transplant waitlist.9 The PELD score at the time of admission were high in all three of these patients, indicating the severity and poor outcome in patients awaiting liver transplant. The case series discussed here included three patients. The underlying cause for acute liver failure was identified as viral hepatitis and autoimmune phenomena in Case 1 and Case 2, as evidence by positive viral serology for hepatitis A and positive ANA (Table 1 and Table 2). In Case 3, the aetiology of acute liver failure was attributed to a metabolic disorder, as indicated by raised methionine level and low cysteine level (Table 3). In addition to PALF, Case 1 and Case 2 had multi-organ dysfunction syndrome. Plasma exchange and CRRT were performed in Case 1 and Case 2; however, in Case 3, only plasma exchange was performed. It is important to note that the time for initiating plasmapheresis was 19 and 10 hours after the patient presented in Case 1 and Case 3, respectively. In contrast, in Case 2 plasmapheresis was initiated at 39 hours of presentation, and unfortunately, the patient died due to refractory shock and multi-organ dysfunction on the fourth day of hospitalisation. The patient was considered for liver transplantation but he could not be transferred to any other hospital due to shock, high inotropes, and rapidly progressive MODS. Larsen et al's study has shown that early use of plasmapheresis (less than 48 hours following ICU admission) showed improvement in different

clinical parameters.[6] In both Case 1 and Case 3, the patients showed significant improvement in bilirubin level, coagulation profile, GCS, and VIS scores after undergoing multiple sessions of plasma exchange. Similar findings were reported by Jørgensen MH et al in their study, suggesting that HVPE is effective in improving the aforementioned laboratory parameters.[14] Complications of PE include hypotension, hypocalcaemia, transfusion-related complications, metabolic alkalosis, and haematoma or catheter site bleeding.[15] No significant complications were observed in Case 1 and Case 2 during plasmapheresis. Case 3 experienced one episode of hypotension and asymptomatic hypocalcaemia which were managed conservatively.

The study findings suggest that early use of plasma exchange may be effective in improving the clinical outcomes of PALF. However, it is important to note that this study was conducted at a single centre with a small number of patients. Further multicentre studies are warranted to validate these findings and to generalise the results to a broader population.

Conclusions

In conclusion, early use of therapeutic plasmapheresis may play an important role as a bridging therapy for liver transplant and for spontaneous regeneration of the patient's liver. Plasmapheresis shows significant improvement in various clinical parameters, including bilirubin levels, coagulation profile, inotropes requirement, and GCS scores. However, questions regarding the optimal timing and frequency of plasma exchange in PALF require further studies to provide more conclusive evidence.

Ethical Approval for publishing the case series were provided by the Ethics Review Committee of the Aga Khan University Hospital, Karachi, Pakistan.

Consent: Consent was taken from child's parents for writing this case series during the hospital stay and on telephonic interaction.

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