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# Therapeutic plasma exchange for mechanical red cell hemolysis: A case series

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## Abstract

We present three cases of severely elevated plasma free hemoglobin (PFH) in pediatric patients on mechanical circulatory support devices at a tertiary pediatric care center. Due to severe levels of PFH in the setting of critical illness with the inability to pursue immediate mechanical device exchange, membrane filtration therapeutic plasma exchange (TPE) was performed, which resulted in a lowering of PFH levels. However, long-term outcomes were heterogeneous across the cases. This case series reviews patient presentation, organ function before and after TPE, and the overall role of TPE as an effective treatment option to decrease severely elevated PFH levels. In doing so, we hope to add to what is known about the use of TPE for mechanical red cell hemolysis and provide guidance on its use in critically ill patients.

### Keywords

mechanical red cell hemolysis; plasma free hemoglobin; therapeutic plasma exchange

## 1 | INTRODUCTION

Mechanical red cell hemolysis and elevated serum plasma free hemoglobin (PFH) levels may be seen in pediatric patients requiring mechanical circulatory support devices.[1–3] Heme pigments released from the degradation of hemoglobin in the kidneys cause acute kidney injury (AKI) via tubular obstruction and direct proximal tubule epithelial cell injury.[4–6] Therapeutic plasma exchange (TPE) has been utilized to reduce PFH to improve associated morbidity.[7–9] However, there is limited data, and mechanical red cell hemolysis is not included in the current American Society for Apheresis guidelines.[10] The objective of this case series is to describe the clinical course of three children who received TPE for elevated PFH secondary to mechanical red cell hemolysis.

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CONFLICT OF INTEREST STATEMENT

Shina Menon serves as a consultant for Medtronic and Nuwellis. Other authors declare no conflict of interest.

## 2 | CASE PRESENTATION

Three pediatric patients at a tertiary care center underwent TPE for elevated PFH secondary to mechanical red cell hemolysis during the years 2020 to 2021 (Table 1). The following data was collected via retrospective chart review. All patients underwent membrane filtration TPE utilizing a Prismaflex device and Baxter TPE 2000 filter (Baxter International, Deerfield, IL) using 1 to 1.3 total plasma volume exchange according to institutional protocol. This study was approved by the center's Institutional Review Board, and written informed consent was waived.

### 2.1 | Case 1

A 3 kg female infant with hemorrhagic shock secondary to placental venous sinus rupture and severe hypoxic-ischemic encephalopathy was placed on venoarterial extracorporeal membrane oxygenation (VA-ECMO) on day of life (DOL) 1, with pump flows of 110 to 120 mL $kg^{-1}$ $min^{-1}$. Due to severe AKI with minimal urine output, she was started on continuous renal replacement therapy (CRRT) on DOL 3. The patient's serum creatinine before CRRT initiation was 1.5 mg/dL. A PFH level of 225 mg/dL (normal range 1–21 mg/dL) was noted 24 h after ECMO initiation and peaked at 628 mg/dL on ECMO day 4. Due to clinical instability preventing ECMO circuit change and to avoid further pigment-mediated damage in the kidney, membrane filtration TPE was initiated. Prismaflex with TPE 2000 filter was connected in series with ECMO and CRRT circuit. Systemic anticoagulation with heparin was continued, and 1.3 plasma volume exchange was performed with fresh frozen plasma as replacement fluid. The post-procedure PFH was 427 mg/dL. Due to a rise in the PFH levels, two additional TPE sessions were completed using a similar prescription on subsequent days, and the PFH level following the third session was 187 mg/dL. No additional TPE was performed, and no adverse events were reported. The patient was decannulated from ECMO on day 7 but continued to require CRRT due to persistent renal dysfunction with oligoanuria until her death on DOL 41 from complications of severe hypoxic-ischemic birth injury.

### 2.2 | Case 2

A 3-day-old, 3 kg male infant born with congenital diaphragmatic hernia was placed on VA-ECMO shortly after birth, with pump flows of 140 to 180 mL $kg^{-1}$ $min^{-1}$. The PFH level at ECMO initiation was 33 mg/dL. Over the course of 3 days, PFH rose to 423 mg/dL. In addition, the patient demonstrated worsening clinical instability, preventing ECMO circuit exchange with evolving fluid overload. TPE was done in series with ECMO, using bivalirudin anticoagulation. The patient underwent 1.1 plasma volume exchange with 5% albumin replacement. The serum creatinine before the procedure was 0.9 mg/dL in the setting of decreasing urine output that was dark in appearance. Urine myoglobin was not measured. The post-procedure PFH was 221 mg/dL. No TPE-related adverse events were observed. Following TPE, CRRT was initiated for severe AKI and fluid overload with serum creatinine measuring 0.8 mg/dL before CRRT initiation. The patient remained critically ill overnight with worsening metabolic acidosis. The following day (DOL 5), PFH rose to 320 mg/dL. However, the patient was found to have an intraventricular hemorrhage, prompting withdrawal of life-sustaining therapies.

### 2.3 | Case 3

An 11-year-old, 35 kg female with Holt-Oram syndrome, complete heart block requiring pacemaker placement, and AKI with oligoanuria on CRRT for 40 days underwent Impella left ventricular assist device (LVAD) placement for significant cardiac dysfunction. The initial PFH level after LVAD placement was 18 mg/dL, but rapidly increased to 297 mg/dL in less than 24 h. Given her future heart transplant candidacy, TPE was recommended to prevent further pigment injury to the kidney. TPE was performed in series with CRRT, with systemic bivalrudin anticoagulation, and 1.3 plasma volume exchange with 5% albumin replacement. The post-procedure PFH was 36 mg/dL. No adverse events related to the procedure occurred. Due to the persistent risk of a rise in PFH with the Impella LVAD, she underwent conversion to Heartware LVAD and right ventricular assist device oxygenator the following day, with subsequent PFH levels measuring <50 mg/dL. The patient received an additional 78 days of CRRT for persistent AKI and sustained oligoanuria before receiving a simultaneous heart-kidney transplantation.

## 3 | DISCUSSION

TPE was safely used to reduce severely elevated PFH levels in three pediatric patients with risk factors for significant tissue toxicity. Due to the severity of illness amongst patients in this case series, the impact of reducing PFH on clinical outcomes could not be ascertained.

Two patients in this case series had severe AKI requiring CRRT before the rise in PFH. Heme pigments can cause direct tubular injury, tubular obstruction, and lead to AKI. Numerous studies show the association of elevated PFH with AKI, and other adverse outcomes in patients on ECMO.[1–4] In addition, Betrus et al showed enhanced hemolysis during combined ECMO and CRRT compared with ECMO alone.[11] In a retrospective analysis of patients requiring ECMO (n = 207, median age 0.13 years), those with severe hemolysis (defined as peak PFH > 100 mg/dL) had greater odds of mortality in the intensive care unit (adjusted odds ratio [aOR]: 5.93; 95% confidence interval [CI]: 1.64–21.43) and hospital (aOR 6.34; 95% CI: 1.71–23.54).[12] Another single-center, retrospective study of children <3 years of age (n = 104) requiring ECMO after cardiac surgery demonstrated higher peak PFH level was associated with increased mortality risk in those who required CRRT and worse renal function amongst those not requiring CRRT.[13] However, data on long-term kidney outcomes associated with elevated PFH in children are limited. Borasino et al showed that elevated PFH levels (>90 mg/dL) were associated with persistent AKI and prolonged renal replacement therapy in children, although the severity of chronic kidney disease was not examined.[1] While there are no data showing the association of PFH with long-term kidney outcomes, given increasing awareness of the connection between AKI and chronic kidney disease, mechanical hemolysis and PFH a potential modifiable risk factors in this population.

Given the risk for AKI and mortality, we suggest daily monitoring of PFH for children at risk for mechanical red cell hemolysis, including children requiring ECMO or LVAD support. TPE may be considered when PFH levels measure greater than 100 to 150 mg/dL and other treatable conditions, including high pump speed, venous cannula displacement, kinks in vascular access, or need for extracorporeal circuit change, have been addressed.

While membrane filtration TPE was performed in all cases in this series in accordance with the institutional protocol for tandem extracorporeal therapies (in series with ECMO and/or CRRT), centrifugal TPE is equally effective in lowering PFH and can be utilized in these situations. If PFH remains elevated after two to three sessions of daily TPE, we recommend additional evaluation and/or replacement of the mechanical device.

Patients in this case series did not demonstrate a change in kidney function after the reduction of PFH. However, all patients had a complex medical history and multiple reasons for AKI. In addition, TPE was initiated at peak PFH levels much higher than what has been associated with adverse effects. Given the risks of elevated PFH levels, additional studies are needed, along with guidelines on the use of TPE for mechanical red cell hemolysis.

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## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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**TABLE 1**

Clinical characteristics of pediatric patients receiving therapeutic plasma exchange for mechanical red cell hemolysis.

| Characteristics | Case 1[a] | Case 2 | Case 3 |
|---|---|---|---|
| Age | 5 days | 3 days | 11 years |
| Sex | Female | Male | Female |
| Underlying diagnosis | Hemorrhagic shock, severe HIE | CDH | Cardiac arrest |
| Mechanical circulatory support device | VA-ECMO | VA-ECMO | LVAD |
| Duration of mechanical circulatory support before TPE (days) | 4 | 3 | 1 |
| Peak PFH (mg/dL) before TPE | 628 | 423 | 297 |
| Post-initial TPE session PFH (mg/dL) | 427 | 221 | 36 |
| Number of TPE sessions | 3 | 1 | 1 |
| Replacement fluid | Fresh frozen plasma | 5% albumin | 5% albumin |
| Oligoanuria before TPE | Yes | No | Yes |
| Need for CRRT before TPE | Yes | No | Yes |
| Duration of CRRT before TPE (days) | 2 | NA | 40 |
| Total duration of CRRT (days) | 41 | 2 | 118 |
| Outcome | ECMO decannulation | IVH | LVAD exchange |

Abbreviations: CDH, congenital diaphragmatic hernia; CRRT, continuous renal replacement therapy; HIE, hypoxic-ischemic encephalopathy; IVH, intraventricular hemorrhage; LVAD, left ventricle assist device; PFH, plasma free hemoglobin; TPE, therapeutic plasma exchange; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

[a]Case 1 underwent a total of three TPE sessions.