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Original Article

Transfusion Medicine Section

Effectiveness of Therapeutic Plasma Exchange in Paediatric Atypical Haemolytic Uremic Syndrome: A Cohort Study in a Transplant Institute of Gujarat, India

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ABSTRACT

Introduction: Atypical Haemolytic Uremic Syndrome (aHUS) is a rare but serious condition that primarily affects the kidneys, leading to kidney failure, anaemia, and low platelet counts (thrombocytopenia). Therapeutic Plasma Exchange (TPE) is the first-line treatment for aHUS, as stated in the American Society of Apheresis Guidelines (ASFA 2023), and is classified as a Category 1 indication.

Aim: To determine whether TPE can be regarded as an effective treatment modality alongside conservative management in paediatric aHUS.

Materials and Methods: This retrospective observational cohort study was conducted in the Department of Transfusion Medicine at the Institute of Kidney Diseases and Research Centre, Ahmedabad, Gujarat, India, between October 2023 and April 2024, involving paediatric patients with aHUS. Anti-Factor H antibody testing was performed to confirm the diagnosis; for some patients, the diagnosis was corroborated through clinical correlation by the treating paediatric nephrologists. The patients were then advised to undergo TPE in conjunction with conservative management. TPE was performed on the Com Tec, Fresenius Kabi, continuous cell separator apheresis machine after obtaining informed consent from the patients' parents or guardians. Pre and post procedural haematological and renal parameters were recorded and analysed to study the recovery profile in each patient. The mean and standard deviation were calculated for all parameters using Microsoft Excel 2010, and certain data were analysed as percentages. A paired t-test was employed to assess the statistical significance of changes in pre and post exchange haemoglobin levels, platelet counts, and serum creatinine levels.

Results: In the present study, 12 paediatric aHUS patients were evaluated for their response to TPE. Of these, the majority showed a positive response to TPE therapy, with 75% of patients (9 out of 12) achieving a complete response. Additionally, 16.66% (2 out of 12) exhibited a partial response to TPE therapy, while 8.33% (only 1 out of 12) showed no response to TPE therapy. Each patient underwent a minimum of eight and a maximum of 16 TPE procedures, culminating in a total of 133 procedures performed on the 12 patients. Adverse events were observed in 25.56% (34 out of 133) of the total TPE procedures. The most common adverse event was chills and rigors, which accounted for 47.05% (16 out of 34 events) of the total number of adverse events.

Conclusion: In the present study, the clinical triad of the disease (haemoglobin levels, platelet count, serum creatinine) improved post-TPE in the majority of patients with aHUS. The adverse events were few and manageable with conservative treatment. It was observed that TPE can be regarded as an effective and safe therapeutic modality for treating paediatric aHUS patients. However, given the small sample size and retrospective nature of the study, more robust prospective studies and clinical trials are needed to draw general conclusions.

Keywords: American society of apheresis guidelines, Anti-factor H antibody, Kidney disease, Thrombocytopenia

INTRODUCTION

aHUS is a rare but serious condition that primarily affects the kidneys, causing kidney failure, anaemia, and low platelet count (thrombocytopenia). Atypical HUS is caused by the abnormal activation of the immune system, which leads to damage to the small blood vessels (microangiopathy). aHUS is often associated with genetic mutations affecting the complement system, a part of the immune system responsible for controlling inflammation and responding to infections. In many cases, these mutations cause the immune system to attack the body's own cells, leading to the problems seen in aHUS. The main features of aHUS include haemolytic anaemia, thrombocytopenia, and kidney damage [1,2].

TPE is the first line of treatment in aHUS, as mentioned in the American Society of Apheresis Guidelines (ASFA 2023), and is classified as a Category 1 indication [3]. In aHUS, TPE helps by removing mutated factors along with other triggers (cytokines) of endothelial dysfunction present in the plasma of the patient, while simultaneously delivering high quantities of Fresh Frozen Plasma (FFP) containing normal factor H and complement factors [4].

These procedures are technically challenging in the paediatric age group due to low blood volume, difficult venous access, and poor patient compliance during the procedure. The present study experience is drawn from the largest tertiary care kidney institute in western India.

MATERIALS AND METHODS

This retrospective observational cohort study was conducted in the Department of Transfusion Medicine at the Institute of Kidney Diseases and Research Centre, Ahmedabad, Gujarat, India, where TPE is routinely performed for various indications. This retrospective study was based on an analysis of the records of TPE procedures conducted in paediatric age group patients with atypical HUS between October 2023 and April 2024. The study was approved by the Ethics Committee of the Institution, with reference number GUTS-IEC/9(ii)/178. Total 12 paediatric patients were included in the study.

Patients in the paediatric age group who were clinically diagnosed with aHUS and admitted under the Department of Paediatric Nephrology were referred to the Department of Transfusion Medicine for TPE. The diagnosis of aHUS was based on the presence of microangiopathic haemolytic anaemia, thrombocytopenia, and acute renal injury in the absence of a diarrhoeal prodrome. Anti-Factor H antibody testing was conducted to confirm the diagnosis; in some patients, the diagnosis was subjectted to clinical correlation as determined by the treating paediatric nephrologists. The patients were then advised to undergo TPE alongside conservative management.

Study Procedure

TPE was performed using a Com Tec, Fresenius Kabi, continuous cell separator apheresis machine after obtaining informed consent from the patients' parents or guardians. Procedures were conducted either daily or on alternate days, depending on the clinical condition and response to TPE therapy, in terms of improvement in clinical and laboratory profiles. During each procedure, 1-1.5 patient plasma volumes were exchanged using FFP as the replacement fluid. The TPE kit was primed with ABO group-specific and cross-match compatible Packed Red Blood Cells (PRBC) if the extracorporeal volume exceeded 10% of the patient's total body volume (in this machine and kit, the extracorporeal volume is 160 mL).

A prophylactic calcium gluconate drip diluted in Normal Saline (NS) (approximately 10-20 mL in 100 mL NS, depending on the weight of the patient) was administered during all TPE sessions. This also included premedication comprising injection pheniramine maleate and injection paracetamol, as advised by the treating paediatric nephrologists. Details of any adverse reactions were also noted. The pre (baseline, before the start of TPE therapy) and post TPE (at the end of TPE therapy) haematological parameters (haemoglobin, Lactate Dehydrogenase [LDH] level, platelet count) and renal parameters (serum urea and creatinine, urine output) were recorded and analysed for each patient.

Based on the response to TPE, as revealed by the laboratory profile after TPE therapy, the patients were divided into three groups: complete responders (Group I), partial responders (Group II), and non responders (Group III), as shown in [Table/Fig-1] [2].

Responders	Haematological profile	Renal profile
Complete (Group I)	Platelet count ≥100*10^9/L at two consecutive occasions, stabilised haemoglobin, LDH < twice normal or normal	RFTs < twice normal or normal
Partial (Group II)	Platelet count ≥100* 10^9/L, at two consecutives occasions, stabilised haemoglobin, LDH < twice normal or normal	RFTs > twice normal
Non (Group III)	Platelet count <100 * 10^9/L, fall in haemoglobin, LDH > twice normal	RFTs > twice normal

[Table/Fig-1]: The three groups of responders. Normal range of platelet count=150-400 * 10^9/L, LDH=140-280 U/L, Serum urea=5-20 mg/dL, and Serum creatinine=0.74 to 1.35 mg/dL (males), 0.59 to 1.04 mg/dL (females) [2].

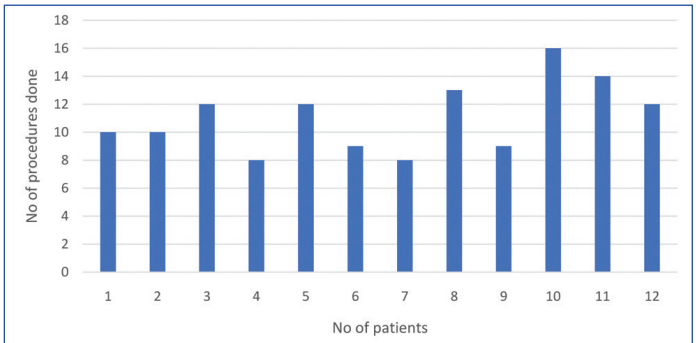
Group I patients demonstrated an improvement in both their haematological and renal profiles after TPE. In group II, only the haematological profile showed improvement. In group III, although a difference between pre and post TPE laboratory values was present, the post TPE therapy parameters did not fall within the acceptable criteria to be considered either partial or complete responders.

STATISTICAL ANALYSIS

The mean and standard deviation were calculated for all parameters using Microsoft Excel 2010. Certain data were analysed as percentages. A paired t-test was used to assess the statistical significance of changes in pre and post exchange haemoglobin levels, platelet counts, and serum creatinine levels.

RESULTS

A total of 12 paediatric patients diagnosed with aHUS, with an average age of 7.6 years (range: 5-16 years), who underwent TPE, were included in this study. There were nine males and three females. The average number of procedures performed per patient was 11.08±2.39 (ranging from 8 to 16) culminating in a total of 133 procedures, as shown in [Table/Fig-2].

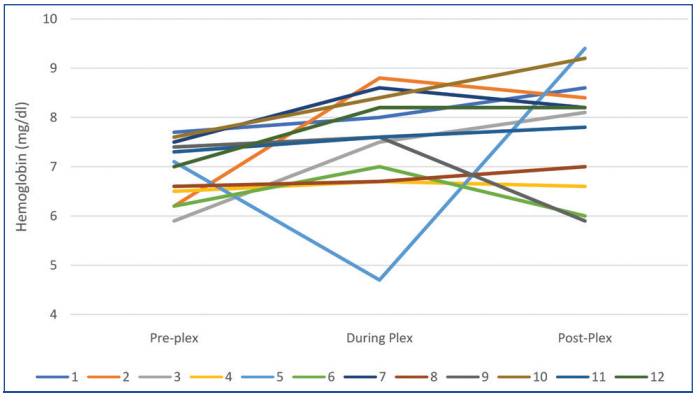


[Table/Fig-2]: Total number of procedures done in each patient.

In the present study, out of the 12 patients, the majority showed a positive response to TPE therapy, with 75% of patients (a total of 9 out of 12) categorised as group I responders, 16.66% of patients (2 out of 12) belonged to group II and showed a partial response to TPE therapy, while 8.33% (only one patient) showed no response. In group II, the two patients had serum creatinine levels twice the normal range following nine and 12 sessions of TPE, respectively. In the only patient belonging to group III, after 11 sessions of TPE over a period of 15 days, the patient's serum creatinine level was 2.80 mg/dL and the LDH level was 664 U/L. This patient did not respond to TPE and therefore, alternative modalities of medical management were pursued.

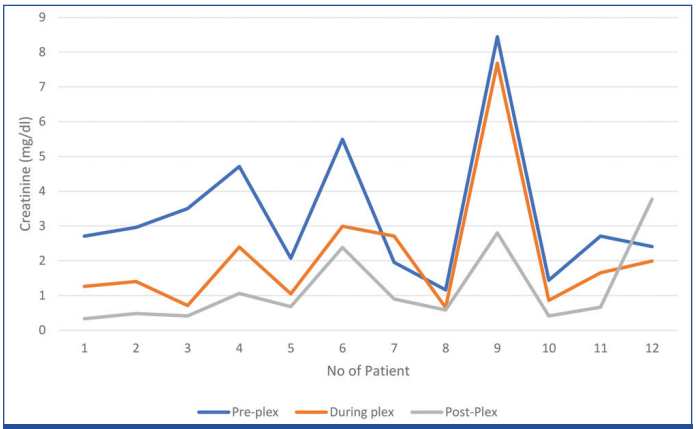
Analysis of the clinical triad of atypical HUS, i.e., haemoglobin levels, serum creatinine levels, and platelet counts, was conducted for each of the patients for pre TPE, during TPE, and post TPE periods, respectively. The median TPE procedure was considered for the purpose of analysing the during TPE parameters in each of the patients.

As seen in [Table/Fig-3-5], TPE resulted in a stabilised increase in haemoglobin levels as well as platelet counts, alongside a decrease in serum creatinine levels in all of the patients. The only exception was patient number 6, who fell into group III and exhibited a decrease in both haemoglobin and platelet counts, with post-last TPE session serum creatinine levels twice the normal range. Additionally, in patient number 5, the pre TPE haemoglobin level was 7.1 mg/dL; however, an investigation after the fifth TPE procedure showed a sudden drop in haemoglobin levels to 4.7 mg/dL. With accelerated haemolysis, which varies from patient to patient, a total of 12 TPE procedures were performed for this patient, and complete remission was achieved, placing the patient in the category of group I. During this period, the patient was diagnosed with septicaemia and treated with broad-spectrum antibiotics. This, along with accelerated haemolysis, could explain the drop in haemoglobin levels by upto 2 mg/dL. Except for the group III patient with no response, the mean

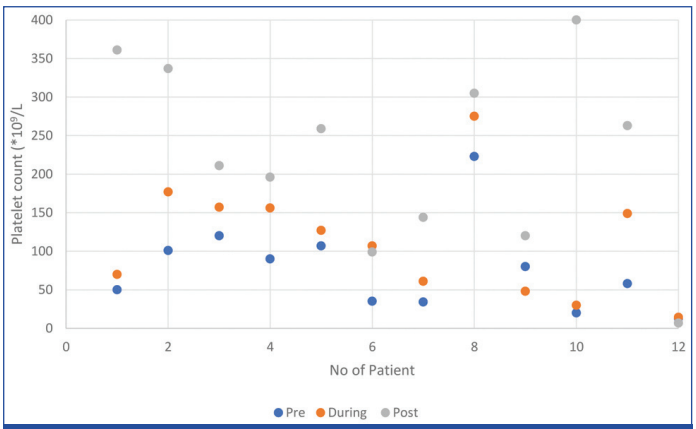


[Table/Fig-3]: Haemoglobin trends seen in each of the patients, pre, during and after plasma exchange.

increase in haemoglobin level among the remaining 11 patients was 1.11 mg/dL, with a standard deviation of 0.84 mg/dL. The increase in haemoglobin levels post TPE was statistically significant, with a p-value <0.01. Similarly, the mean increase in platelet counts was 158×10^9/L±119×10^9/L, which was also statistically significant, with a p-value <0.04. Lastly, the mean decrease in serum creatinine levels was 2.31 mg/dL, with a standard deviation of 1.42 mg/dL, exhibiting statistical significance with a p-value <0.01. Despite the statistically significant outcomes in these parameters post-TPE, two patients belonged to group II (partial response) and one patient belonged to group III (no response), as defined in [Table/Fig-1] [2].



[Table/Fig-4]: Creatinine trends seen in each of the patients, pre, during and after Plasma exchange.



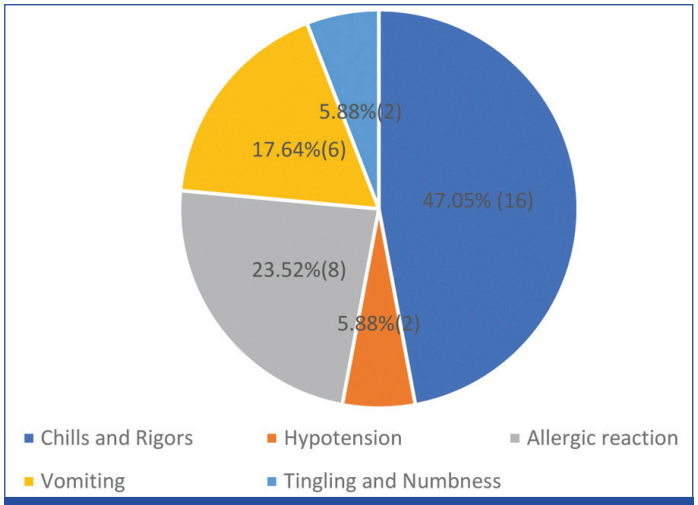
[Table/Fig-5]: Platelet counts seen in each of the patients, pre, during and after Plasma exchange.

Adverse Events

Out of a total of 133 TPE procedures performed in 12 patients, adverse events were observed in 34 procedures (25.56%). The most common adverse event was chills and rigors, which were experienced in 16 procedures (47.05% of the total adverse events). This was followed by allergic reactions, observed in 8 (23.52%) procedures out of the total adverse events. Vomiting occurred in 6 (17.64%) procedures, and tingling numbness of the peripheries was noted in 2 (5.88%) procedures. Lastly, hypotension was also seen in 2 (5.88%) procedures of all adverse events. These adverse events were managed according to our standard operating protocol and in consultation with the treating paediatric nephrologists, with the TPE procedure being completed in all cases. [Table/Fig-6] depicts the types of adverse events seen in the 34 procedures along with their distribution.

DISCUSSION

Our institute is a large tertiary care kidney centre in western India that receives patients from various parts of the region. A total of 133 TPE procedures were carried out on 12 paediatric aHUS patients over a period of seven months. We observed an overall complete response rate of 75% and a partial response rate of 16.66%, which is similar to the response reported by Paglialonga F et al., in HUS/TTP patients, and higher than that reported by Caprioli J et al., (67%) [5,6].



[Table/Fig-6]: Distribution of the type of adverse events seen.

In the present study, the adverse event rate was 25.56%, which is comparable to that observed by Paglialonga F et al., using a similar apheresis technique, but lower than that reported with membrane filtration [5]. The adverse event rate in paediatric patients undergoing TPE in the literature ranges from 13.8% [7] to 55% [8], which is considerably higher than in the present study. However, the small sample size in this study may be a confounding factor when drawing inferences about the rate of adverse events. Conversely, the adverse event rate in paediatric patients in the present study is comparable to that expected in adults [9,10].

The most common adverse reaction observed in this study was chills and rigors, which is similar to findings in the study by Sinha A et al., involving membrane filtration [11]. This can be attributed to the transfusion of FFP during TPE in patients with aHUS. Although the FFP is thawed at 37 degrees prior to transfusion, some patients may experience mild to moderate chills and/or rigors. These symptoms are conservatively managed with antihistamines and the use of blankets or heat warmers, which provide relief to the patients.

Another commonly observed reaction is allergic reactions, which can involve the development of rashes and urticaria. These reactions can also be managed conservatively in consultation with the treating clinician and are mainly attributed to an allergy to the transfusion of FFP during the procedure. During TPE, Acid Citrate Dextrose solution is used as an anticoagulant in the sterile kit, and a small amount is infused into the patient. Citrate, when in the bloodstream, chelates calcium ions, leading to hypocalcaemia, which can cause symptoms such as tingling, numbness, and, in a few patients, vomiting. These symptoms can be managed with the infusion of supplemental calcium gluconate solution and antiemetic drugs, if required.

As large volumes of fluid shift during TPE, haemodynamic instability is inevitable. This instability may sometimes result in hypotension, which can be managed with simultaneous saline infusion and close monitoring of the patients. All observed adverse events during TPE are mild and manageable with appropriate medical treatment.

On comparing studies involving paediatric patients based on the centrifugation method with those based on membrane filtration, it has been observed that TPE performed with current automated apheresis devices is more efficacious and safer, and presents a definite advantage. Indeed, the current ASFA guidelines [3] state that TPE therapy for aHUS is accepted as a first-line treatment, either as a primary standalone therapy or in conjunction with other treatment modalities.

However, the quality of evidence is low, as no randomised control trials have been conducted regarding interventions for aHUS in paediatric patients. Additionally, there are no prospective studies addressing the issues of the number and duration of TPE required to achieve complete or partial remission.

More prospective studies and randomised control trials are needed to strengthen the evidence and establish standard guidelines for the use of TPE in aHUS. Furthermore, critically ill patients requiring ventilatory support and experiencing end-organ damage due to aHUS were not included in this study. These patients comprise a small but crucial segment of the variable syndrome that aHUS represents. The outcomes of TPE in critically ill aHUS patients need to be studied in depth to reach a general consensus.

Limitation(s)

This retrospective observational cohort study also has similar limitations, including a small sample size and its retrospective nature. Therefore, the results cannot be extrapolated to formulate a standard approach for TPE in aHUS.

CONCLUSION(S)

In the present study, the majority of patients responded positively and achieved complete or partial remission following TPE. The adverse events were few and manageable with conservative treatment, and did not outweigh the advantages of this procedure. This study has several limitations; its retrospective nature and small sample size pose constraints in providing solid evidence. However, there is a general consensus that TPE can be regarded as an effective and safe therapeutic modality for treating paediatric aHUS patients.

Ethics Approval

This study was conducted in accordance with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Institute of Kidney Diseases and Research Centre (Date: 09/11/24; GUTS-IEC/9(ii)/178).

Availability of Data and Materials

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

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