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Efficacy of cascade plasmapheresis in comparison with conventional therapeutic plasma exchange for relapsed atypical hemolytic uremic syndrome: A case report

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Abstract:

Atypical hemolytic uremic syndrome (aHUS) is a rare and life-threatening disease that is associated with high mortality and morbidity. The incidence of aHUS is about 1 or 2 cases per 1,000,000 per year. Etiology can be either familial or sporadic. The pathogenesis of aHUS involves dysregulation of the alternative complement pathway, with predisposing mutations in complement genes. aHUS has a poor prognosis and a gradual or a relapsing (30%–86%) clinical course. The disease may present at any age but is mostly seen in children and young adults. Therapeutic plasma exchange (TPE) is one of the primary modalities of treatment in aHUS. This report presents the utilization of cascade plasmapheresis and its advantages over TPE in a patient with relapsed aHUS. There was a 73% decrement in antifactor H antibody levels following cascade plasmapheresis.

Keywords:

Atypical hemolytic uremic syndrome, cascade plasmapheresis, thrombotic microangiopathy

Introduction

Hemolytic–uremic syndrome (HUS) is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. It is classified as typical and atypical HUS (aHUS). Typical HUS is associated with verocytotoxin-producing *Escherichia coli* and *Shigella dysenteriae* type 1.[1] aHUS is complement-mediated thrombotic microangiopathy (TMA) caused by uncontrolled complement activation due to genetic mutations in the alternative pathway of complement.[2,3] It is associated with a 25% mortality rate and the majority of the patients' progress toward end-stage renal disease (ESRD).[4] The management of these cases can be very challenging. Eculizumab, a humanized monoclonal antibody, inhibits the terminal part of the complement pathway by binding to complement protein C5.[5] It is the drug of choice in aHUS. If eculizumab is not available, therapeutic plasma exchange (TPE) is the alternative therapy to remove circulating factors. The principle of plasma exchange is to replace abnormal antibodies against circulating complement regulators, such as complement factor H with normal plasma.[6] generally, conventional TPE is used for treating these cases. We aimed to assess the efficacy of cascade plasmapheresis (CPA) in a patient with relapsing aHUS.

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Case Report

A 12-year-old boy with no premorbidities presented with complaints of vomiting, easy fatigability, and oliguria. Clinical examination was normal and laboratory parameters showed features of anemia, signs of hemolysis (schistocytes) in peripheral smear. Deranged renal functional test (RFT) (urea – 138 mg/dl, serum creatinine – 5.2 mg/dl) and elevated lactate dehydrogenase (LDH) (1025 IU/L) were also noted. Urine analysis was suggestive of proteinuria with microscopic hematuria. A renal biopsy was done which showed TMA with no evidence of necrosis or crescents. As part of an evaluation of aHUS, antifactor H antibody levels were done and found to be high (8000 AU/mL, normal: 0–100 AU/mL). The patient was diagnosed to have complement-mediated (antifactor H antibody) TMA. Because of the worsening renal function, he was put on dialysis. TPE was initiated for the management of TMA. Ten procedures of conventional TPE were done. He was started on immunosuppressive therapy (prednisolone and azathioprine) and antihypertensive medications. The patient recovered and was in hematological and clinical remission for 4 years till 2018.

Relapse of atypical hemolytic uremic syndrome

In March 2018, the patient presented with signs of relapse. The laboratory evaluation showed signs of anemia, thrombocytopenia, hemolysis (spherocytes and schistocytes were noted on peripheral smear), and elevated LDH (1200 U/dl). We observed nephrotic range proteinuria (24 hour proteins- 4.5 grams), and elevated serum creatinine and blood urea. The clinical profile, laboratory parameters, and anti-factor H levels were serially monitored. Antifactor *H*-test was done using enzyme-linked immunosorbent assay by VIDITEST kit. The patient was started on mycophenolate mofetil (500 mg) and corticosteroids. Institutional ethics committee clearance was obtained for the study (IEC-No-05-2021), and informed consent from the patient was also obtained.

Conventional therapeutic plasma exchange

TPE was initiated, and a total of 64 (8 cycles) conventional TPE procedures were performed over 1 ½ years (2018–19) using an apheresis machine (COM. TEC – Fresenius Kabi). Each cycle involved eight procedures of TPE. The mean value of total blood volume processed in a procedure was 4888 ml, and replacement volume was 4235 ml, with a mean plasma volume fraction of 1.3 TPV. The replacement fluids used were fresh frozen plasma (FFP), 6% albumin and 0.9% normal saline. Acid-citrate-dextrose A was used as anticoagulant for all the procedures. We noted a 52% reduction in the antifactor H levels following a cycle of TPE. The mean value of antifactor H levels pre- and post-TPE cycle was 379.54 ± 269.64 AU/mL and 189.73 ± 172.12 AU/mL, respectively (P = 0.11). Remission was not achieved after eight cycles of TPE, hence, we initiated CPA.

Cascade plasmapheresis

A total of eight CPA procedures were done over the next 1 year using Evaflux 2A20 plasma fractionator (Kawasumi Laboratories Inc., Japan). Total blood volume processed was 9112 ml, with a mean plasma volume fraction of 2.1 TPV. The mean value of antifactor H levels pre- and post-CPA was 450.65 ± 392.19 AU/mL and 135.44 ± 153.13 AU/mL, respectively. Antifactor H levels were performed before and after each procedure of CPA. We noted a 73% decrement of antifactor H levels after each procedure of cascade plasmapheresis.

The comparison of pre- and postconventional and cascade plasmapheresis laboratory parameters are given in Table 1. As shown in Figure 1, we noted decrement in antifactor H levels following the therapeutic procedures and the overall percentage reduction was higher with cascade plasmapheresis.

Discussion

Complement-mediated thrombotic microangiopathy is caused by uncontrolled activation of the alternative complement system. TMA is a process in which there is a pathological insult to endothelial cells of end organs leading to the formation of fibrin-platelet microthrombi.[1] Complement activation is central to

Table 1: Mean pre- and postprocedure-therapeutic plasma exchange and cascade plasmapheresis laboratory parameters

Parameters	Normal ranges	Therapeutic plasma exchange		Cascade plasma exchange	
		Preprocedure	Postprocedure	Preprocedure	Postprocedure
Hemoglobin (g/dL)	13-17	8.13±0.79	7.96±0.8	9.165±1.42	9.11±1.36
Hematocrit (%)	40-50	24.17±2.28	23.57±2.07	27.10±3.51	27.045±3.33
Platelet count (cells/ µL)	150,000-400,000	207,652±65,229	210,065±56,941	256,895±47017	258,737±50,310
LDH (IU/L)	125-220	384.65±107.11	281.30±90.61	379.44±76.78	264.22±75.8
Urea (mg/dL)	16.6-48.5	126.93±36.41	123.2±34.08	109.44±25.45	106.06±20.12
Creatinine (mg/dL)	0.7-1.2	4.14±1.79	4.03±1.71	2.78±0.44	2.74±0.44

LDH=Lactate dehydrogenase

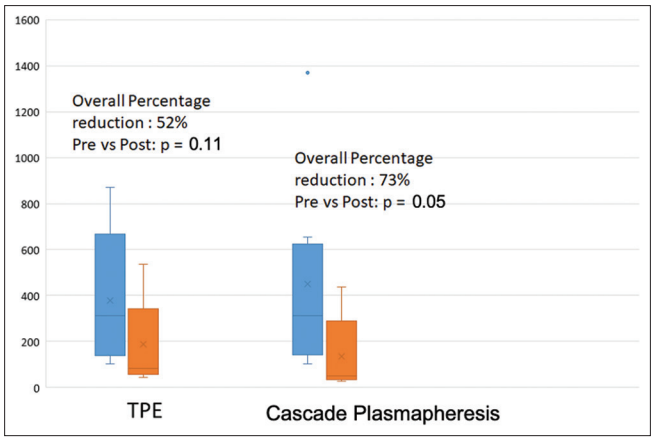

Figure 1: Percentage reduction of antifactor H levels in therapeutic plasma exchange and cascade plasmapheresis. X on whisker plot represents the mean, the overall percentage reduction was mean decrement of anti-factor H

the pathogenesis of aHUS. The rates of mortality and progression to ESRD are approximately 25% and 50%, respectively.[7] Genetic mutations and polymorphisms, primarily involving complement regulatory proteins, predispose to complement-mediated TMA. Mutations of the complement factor H gene, which encodes a regulatory protein in the alternative complement pathway, and CFH-related proteins are the most frequently identified genetic abnormalities in patients with complement-mediated HUS. Complement factor H in conjunction with complement factor I competes with complement factor B for C3b binding and accelerates C3 convertase decay.[8] Complement factor H mutations are the most frequent (20%–30%).[7,9]

Conventional TPE removes plasma proteins including albumin and immunoglobulins nonselectively and requires a high amount of replacement fluid. CPA is one of the extracorporeal methods of antibody removal. The plasma is separated from cellular components by centrifugation, and then, the plasma is allowed to pass through a second filter. This results in the removal of high-molecular-weight substances and the rest of the products go back to circulation.[10,11]

CPA is indicated for hypercholesterolemia and is a part of a preconditioning regimen for ABO-incompatible liver and renal transplants.[10] It selectively removes macromolecules such as immunoglobulin G, immunoglobulin M, immunoglobulin A antibodies, coagulation factor inhibitors, low-density lipoprotein, very LDL, lipoprotein (a), and immune complexes. Replacement fluid (albumin or FFP) is not required for CPA, and thus, the associated side effects such as allergic reactions can be avoided. The patient's plasma recirculates through the column and is returned with all the vital plasma solutes, preventing the deficiency of clotting factors.[11]

To the best of our knowledge, CPA was used as a treatment modality in complement-mediated TMA (antifactor H antibody) for the first time in India. The present report established the efficiency of CPA significantly by reducing the antifactor H levels in the patient leading to a better outcome. As per the American Society for Apheresis guidelines, plasmapheresis is indicated (category I, grade 2C),[7] with further study on efficacy of CPA, we can consider adding up this treatment modality in patients with antibody-mediated TMA.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published, and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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