Plasma Infusion Therapy in Atypical Hemolytic Uremic Syndrome–Long Term Outcome

Rahul Kohli
Sanjeev Gulati

We report 2 boys with atypical (diarrhea negative) hemolytic uremic syndrome requiring dialysis, who recovered complete renal functions after receiving fresh frozen plasma infusion therapy. One patient relapsed and required second course of plasma infusion therapy. After a prolonged follow up, both showed normal renal functions with mild residual hypertension.

Key words: *Atypical hemolytic uremic syndrome, Fresh frozen plasma.*

Atypical hemolytic uremic syndrome in children carries a bad prognosis with a high mortality and residual renal dysfunction in majority of the survivors(1). Plasmapheresis had been the therapy of choice. There are few reports of the efficacy of fresh frozen plasma (FFP) therapy but the long term follow up and the risk of relapse has not been reported so far(2-8). We report long-lasting recovery of renal function after FFP alone in 2 patients with atypical HUS.

From the Department of Nephrology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow 226 014, Uttar Pradesh, India.

Correspondence to: Dr. Sanjeev Gulati, Associate Professor, Department of Nephrology, Sanjay Gandhi Post Graduate, Institute of Medical Sciences, Raebareli Road, Lucknow 226 014, Uttar Pradesh, India. E-mail sgulati@sgpgi.ac.in

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Case reports

A 10-year-old boy presented with history of loss of appetite, weakness, nausea and jaundice for 2 weeks. There was a history of fever and coryza 6 weeks prior to the admission. He had hypertension (130/96 mm Hg), pallor and mild icterus. Laboratory evaluation revealed anemia (hemoglobin 46 g/L), normal total leukocyte count (8.4 × 10^3 cells/dL), normal platelet count (222 × 10^9/L), elevated reticulocyte count (22%), a peripheral blood film demonstrated fragmented red blood cells, elevated creatinine (3.7 mg/dL, normal 0.3-0.7mg/dL), hyperbilirubinemia (3.2 mg/dL), mildly raised ALT (81 IU/L) and AST (53 IU/L) and high lactate dehydrogenase (LDH) (14500 U/L, normal <450 U/L). Serum C3 levels were marginally low (58 mg/dL). Anti-nuclear antibodies and anti-neutrophil cytoplasmic antibodies were not detected and direct Coombs test was negative. Urinalysis showed hematuria and marked proteinuria. Ultrasound revealed bilateral normal sized kidneys with increased echogenicity. A presumptive diagnosis of atypical (diarrhea negative) HUS was made. A renal biopsy was not done as consent was refused. His renal functions worsened and he was given one session of acute peritoneal dialysis along with 3 units of packed red cell transfusion. Nifedipine (40 mg/day) and clonidine (300 mcg/day) were given for hypertension and he received daily FFP infusions (25 mL/kg/day) for 14 days. Gradually, his urine output increased and renal functions improved. He was switched to lisinopril (10 mg/day) and the BP was better controlled. His serum creatinine declined to 0.6 mg/dL by 3 weeks. He continued to have normal renal function and the serum C3 was also normal (85 mg/dL).

On last follow-up, 45 months after the initial episode, blood pressure was well

controlled (100/70 mm Hg) on lisnopril 2.5 mg/day, plasma creatinine was normal (0.7 mg/dL) and urinalysis showed trace proteinuria and no hematuria. No other family members are suffering from HUS or renal disease.

Case 2

An 11-year-old boy presented with 10-day history of nausea, vomiting, decrease in urine output and swelling over face and feet. There was no history of preceding diarrhea. He had hypertension (160/90 mm Hg), mild icterus, pallor, periorbital puffiness and pedal edema. Hematology revealed anemia (hemoglobin 66 g/L), elevated reticulocyte count (6%) and thrombo-cytopenia (53×10^9/L); peripheral blood film showed fragmented red blood cells. Blood chemistry showed increased plasma creatinine 7.4 mg/dL, indirect hyperbilirubinemia (serum bilirubin 2.3 mg/dL), normal ALT (65 IU/L) and AST (68 IU/L) and high LDH levels (10820 IU/L). Complement C3 level was normal, anti-nuclear and anti-nuetrophil cytoplasmic antibodies were not detected and direct Coombs test was negative. Urinalysis revealed hematuria and marked proteinuria (urine spot protein/creatinine ratio 7). Ultrasound revealed bilateral normal sized kidneys with increased echogenicity. Renal biopsy was not done in view of thrombocytopenia, and a presumptive diagnosis of atypical (diarrhea negative) HUS was made. Patient was given one session of hemodialysis in view of advanced renal failure along with packed cell transfusions. Subsequently, he received daily FFP infusions (25 mL/kg/day) for 18 days. Within 2 weeks, urine output increased and renal functions improved (serum creatinine 1.4 mg/dL). He continued to have anemia (hemoglobin 7 g/dL), proteinuria (urine spot protein/creatinine ratio 1.5) but blood pressure was controlled on lisnopril 5 mg/day and he was discharged .

At 4 weeks after discharge, hemoglobin declined to 6.6g/dL, LDH (which had normalized) was found to be elevated (624 IU/L), blood pressure was elevated (160/110 mm Hg) and there was an increase in serum creatinine (3.0 mg/dL). Lisinopril was stopped and atenolol 50 mg and amlodepine 10 mg were required for blood pressure control. Renal biopsy revealed lesions of arteriolar thrombotic micro-angiopathy. Patient was given FFP infusions (30 mL/kg/day) for 20 days. His renal functions improved, LDH levels declined (303 IU/L), hemoglobin improved (9 g/dL) and blood pressure was well controlled. He was switched back to enalapril 5 mg/day and losartan 25 mg/ day.

On last follow-up, 24 months later the boy is in good health. Growth and cognitive development are normal. Renal function is normal (serum creatinine 0.9 mg/dL). There is no hematuria or proteinuria. Blood pressure is well controlled (100/66 mm Hg) on enalapril 5 mg/day and losartan 25 mg/day. There is no history of HUS or renal disease in any other family member.

Discussion

We report long-lasting recovery of renal functions after FFP infusion alone in pediatric atypical HUS. This carries a bad prognosis and is an important cause of end-stage renal failure in children(1,2).

Among the therapeutic modalities available, plasma exchange (plasmapheresis combined with FFP replacement) is currently the treatment of choice. Several reports have confirmed the efficacy of this treatment option in children (3,4). However, it carries substantial morbidity in terms of central venous catheter related as well as complications associated with plasma exchange(5).

Other treatment options for the manage-

ment of thrombotic microangiopathy include use of FFP and cryosupernatant. Significant benefit has been reported with FFP alone with lower rates of complications in TTP(6,7). There are some reports to suggest that the approach may be beneficial in HUS as well(9,10). Although, plasma manipulation does induce hematologic remission, it is not clear whether plasma effectively accelerates renal recovery(9). None of the reports to date have analyzed long-term benefits of FFP alone in children with atypical HUS. Both of our patients have shown long-term remission (45 and 24 months, respectively) of disease activity with normal renal functions and resolution of proteinuria. Mild residual hypertension, well-controlled on drugs, is persistent in both patients.

In conclusion, the present report suggests that FFP alone may be effective in children with atypical HUS with long lasting clinical benefit.

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