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Plasma Volume to Achieve Remission in Atypical Hemolytic Uremic Syndrome

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Introduction: Atypical hemolytic uremic syndrome (HUS) is defined as a heterogeneous group of disorders. Plasma infusion or plasma exchange is the rescue therapy for this life-threatening syndrome. There is no evidence for the volume of plasma required to induce remission.
Materials and Methods: Between 2007 and 2018, Forty – two patients (M=20, F=22) with a diagnosis of recurrent or familial atypical hemolytic uremic syndrome (aHUS) who were admitted to Ali-Asgar Children's Hospital were enrolled in this observational retrospective study. The total volume of plasma required for normalizing platelet (>150000) and LDH (<500 IU), eliminating hemolysis, and decreasing serum creatinine at first presentation of disease was calculated. Patients with TTP, vasculitis, and post infectious HUS were excluded.
Results: The mean age of the patients was 53 months (3-144 m). The majority of patients achieved remission at first presentation by plasma infusion (5 under peritoneal dialysis and 4 under hemodialysis) but ten patients required plasmapheresis. A total of 980 units of FFP perfused with a total volume of 195.975 L. The median (range) total plasma volume required for remission was 166 ml/kg (43-2850 ml/kg).
Conclusions: This study showed that the required plasma volume for the acute phase of atypical HUS for controlling the first attack of disease.

Keywords: Atypical Hemolytic Uremic Syndrome; Plasma Volume; Remission Induction; Child.

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Running Title: Plasma Volume to Achieve Remission in HUS

Introduction

Hemolytic uremic syndrome diagnosed by microangiopathic hemolytic anemia, thrombocytopenia and acute kidney injury [1]. The etiologies classify to infection, vacuities, medications, metabolic disorder, malignancy, post radiation, or complement deregulation. However, eculizumab is recommended as an effective therapy to reduce morbidity and mortality in diarrhea negative HUS; plasma infusion or plasma exchange make the rapid treatment when the eculizumab is not available or affordable.

The recommended volume of plasma infusion is 1.5 times of plasma volume per session till achieve remission then taper it off.

Atypical HUS (aHUS) is a rare heterogeneous disorder. Its pathophysiology includes inability to limit activation of the alternative complement pathway with subsequent damage to systemic vasculature and their endothelial bed in the body [2]. It can present at any time of the year, any age, with or without a positive family history of aHUS It often has an insidious onset and a relapsing

character, and tends to cause severe arterial hypertension [2].

Diagnosis of aHUS is made by clinical and laboratory features and exclusion of other causes of HUS and TTP [2].

Successful management of HUS begins with early diagnosis of the disease and proper supportive care such as appropriate control of the volume status, electrolyte abnormalities, hypertension, and anemia.

According to the 2009 guideline of the European Pediatric Study Group for HUS, plasma therapy is the first-line therapy for atypical HUS (plasma exchange or plasma infusion) [3,4].

The one and only advantage of plasma infusion over plasma exchange is its simpler application. It can be performed in almost any medical facility and does not require specialized equipment, central venous access, or specially trained staff.

Plasma is normally given at a 1.5 times of plasma volume per session (60 ml/kg) for five days and then increase the intervals until the patient remain in remission. This dose can be expected to increase by 20% of Factor Activity in a child without ongoing consumption of coagulation factors [2].

There is no consensus or evidence-based guideline for the effective therapeutic dose or schedule. Most clinicians use a tapering program in which treatment intervals are extended based on the patient's responses. Its most considerable complication is volume overload, especially in patients with reduced renal function. There is no document to show how much of plasma volume actually get the patient to remission.

The aim of this study is to find the volume of plasma that induce remission in aHUS.

Materials and Methods

This was an observational retrospective study between March 2007 and 2018. All patients with diagnosis of atypical hemolytic uremic syndrome (aHUS) admitted in Ali-Asgar Children Hospital included. The inclusion criteria were: 1) aHUS defined by microangiopathic hemolytic anemia (hemoglobin below lower limit of normal for age, negative coomb's test, and increase Lactate Dehydrogenase (LDH), thrombocytopenia (platelet < 150000), and acute kidney injury, 2) no source of any bacterial infection, 3) ADAMT13 > 0.5% 3) Negative results for ANA, anti DNA, C-ANCA, and P-ANCA.

Plasma infusion was started immediately with volume of 5-20 ml/kg/day depends on eGFR and blood pressure. Provided that central vein access was inserted, plasmapheresis with volume of 20-40 ml/kg totally replaced by fresh frozen plasma were done. Plasma therapy continued until remission achieved that was defined by increase platelet level and remained persistently above 150000, LDH return to normal level of <500IU, no drop of hemoglobin, and reduction trend in serum creatinine level. Lab tests were rechecked every day after discontinuation of therapy in order to reassure of recovery. All caregivers gave consent for plasma therapy in either form of infusion or plasmapheresis. The study was according to declaration of Helsinki 2013 and it was approved by AACRDC ethic committee (ID number: 96-04-225-32796). Demographic data, relevant laboratory tests, and the total volume of infused plasma to achieve remission in the first episode of presentation were collected.

Results

Between 2007 and 2018, forty – two patients with diagnosis of aHUS were included. Figure one showed the total number and the reason of exclusion. Table-1 represented the demographic, clinical, and laboratory data of patients.

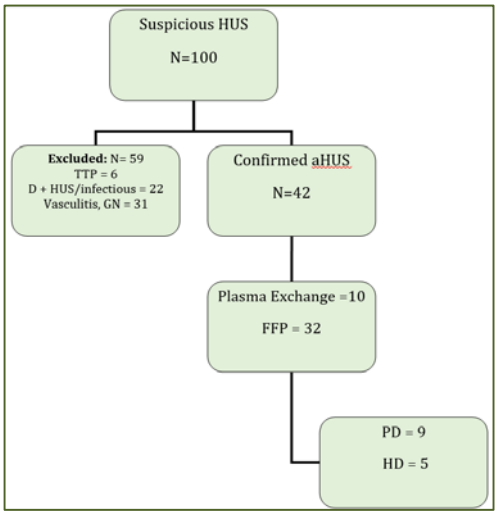

Figure 1. Flowchart of enrolled cases in the study

The total FFP volume infused in each patient was calculated. Accordingly, the highest, lowest, and mean volume was 93.8ml/kg, 166.5ml/kg, and 358 ml/kg, respectively.

Patients with low C3 level required higher FFP infusion by mean (SE) of 584 ml/kg (284) vs 361ml/kg (105) (p-value=0.12).

Table 1. Demographic and laboratory data of Study Cases

	At admission
Gender Male-n(%)	32(76)
Age (months) median (range)	37.5(4-144)
Weight, Kg median (range)	18.5 (6-46)
Height, cm median (range)	100.7(62-151)
SBP, mmHg median (range)	100(80-140)
DBP, mmHg median (range)	70(50-85)
eGFR, ml/min/1,73m^2 median (range)	18.6(9.3-151)
BUN, mg/dl median (range)	55(6-120)
Creatinine, mg/dl median (range)	2.8(0.3-7.7)
Hemoglobin, g/dl median (range)	8.1(6-11.5)
Platelet, x10^3 median (range)	69(4-420)
LDH, IU, median (range)	2270(658-8531)
C3-Low N (%)	10(25)

The volume of FFP infusion was inversely correlated with LDH level, serum creatinine, and platelet count at initial presentation but it was not statistically significant (p-value>0.05)

Discussion

The results of this study suggest the early use of FFP for successful treatment of atypical HUS. Some researchers have shown complete recovery with FFP infusion [5-8] whereas some new studies suggest complement inhibitor agents like eculizumab as adjuvant or rescue treatment [9-11]. Moreover, our study showed that the required plasma volume for the acute phase of recurrent or familial HUS was at least twice the recommended total plasma volume for controlling the acute phase of the disease. Plasma infusion at a dose of 10 to 20 ml/kg/day has been effective in some studies whereas higher volumes of fresh frozen plasma were needed in other studies [12-14].

Some guidelines recommend plasma exchange at 1.5- times the plasma predicted volume (60-75 ml/kg) as an efficient treatment [4,7]; however, some issues such as the complexity of the procedure, need for vascular access, and particular pediatric environment should be considered [15].

Conclusion

Taken together, administration of FFP at a double dose could provide desired outcomes. This treatment is simple and is associated with few side effects in comparison with other available treatments. Nevertheless, further studies are needed to evaluate the most effective dose and duration of treatment.

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Conflict of Interest

We have no conflict of interest to declare.

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