Original Research Paper

Volume-9 | Issue-6 | June-2019 | PRINT ISSN No. 2249 - 555X

Pathology

THERAPEUTIC PLASMA EXCHANGE: GOLD STANDARD TREATMENT FOR ATYPICAL HEMOLYTIC UREMIC SYNDROME IN CHILDREN IN INDIA.

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ABSTRACT

INTRODUCTION: Atypical HUS (aHUS) is a serious disease caused by disorder of the complement system or due to genetic etiology. Therapeutic Plasma Exchange (TPE) is a preferred treatment for aHUS.

MATERIAL AND METHODS: This was a retrospective study carried out over pediatric patients with aHUS between 2017 and 2018. One to 1.5 plasma volume was removed during every TPE and replaced with fresh frozen plasma. Clinical parameters were monitored pre and post TPE.

RESULTS: 119 TPE were carried out in 15 patients. Average pre TPE and post TPE platelet count were 96.53 ± 75.33 x 10^9/L and 116.80 ± 80.30 x 10^9/L(p=0.34) Average pre TPE and post TPE hemoglobin was 6.76 ± 1.79 gm/dL and 8.13 ± 2.12 gm/dL (p=0.5) and pre TPE and post TPE serum creatinine was 1.43 ± 1.85 and 0.70 ± 0.63 mg/dl (p<0.01).

CONCLUSION: TPE is a safe procedure in the treatment of aHUS.

KEYWORDS : Atypical hemolytic uremic syndrome, plasma exchange.

BACKGROUND: Hemolytic uremic syndrome (HUS) is a pathological process of microangiopathic hemolytic anemia (MAHA), acute renal failure and thrombocytopenia [1], often leading to end-organ ischemia and infarction affecting particularly the kidney and brain. When it is associated with infection caused by certain strains of Escherichia Coli producing Shiga-like toxins it is called as STEC-HUS or typical HUS, predominantly affecting children and clinically manifested by severe diarrhea.[1] Atypical hemolytic uremic syndrome (aHUS) is caused by defect in the complement pathway or genetic mutations of factor H that develop altered renal function by formation of abnormal blood clots in small sized blood vessels of kidney.[2] Therapeutic Plasma Exchange (TPE) is an adjuvant treatment modality used to treat aHUS. TPE is the separation of plasma from the cellular contents, its retention and return of the cellular components to the patient.[3,4]

TPE is considered as the first line of therapy (category -I) for aHUS due to factor H autoantibodies, category II for complement factor gene mutations and category IV for membrane cofactor protein mutations, since this factor does not circulate in plasma.[5-7] Fresh Frozen Plasma (FFP) is used as a replacement fluid during TPE in these patients since it provides normal Factor H and complement factors. No specific guidelines are available for TPE in pediatric population. TPE is a challenging procedure in pediatric patients due to poor compliance, small body volume, and difficult venous access.

We present our experience of TPE as an adjuvant treatment modality for aHUS.

MATERIALS AND METHODS

We carried out Institutional Ethics Committee approved retrospective study of children subjected to TPE for aHUS. The study period is from January 2017 to December 2018. All patients with clinical diagnosis of aHUS and high anti-factor H antibody were included in this study and patients suffering from sepsis, seropositivity and advanced systemic illness were excluded.

TPE was performed on two apheresis machines, Fresenius COMTEC–Fresenius Kabi (Germany) and Spectra Optia-Terumo BCT (Lakewood U.S.A). Both the machines are based on the principle of continuous flow centrifugation.

Informed consent was taken from all the guardians. Baseline complete blood count including hematocrit and platelet count were recorded. The machines were primed with normal saline (NS). ABO blood group specific cross matched packed cells (PCV) were used to prime the apheresis machine after priming with NS in two patients with hemoglobin < 5 gm/dl. Acid citrate dextrose to whole blood ratio was 1:12. Dual lumen catheter was inserted in internal jugular vein on either side in all the patients under aseptic and antiseptic precautions. Inlet flow was kept between 45 ml to 50 ml per minute depending on the caliber of the vein. Group specific FFP was used as replacement fluid in all patients. Calcium gluconate 10%, 2ml/kg was given in 150 ml NS and was administered by separate access, throughout the TPE procedure to prevent citrate toxicity. One TO 1.5 plasma volume was removed per TPE session. Temperature, pulse rate, blood pressure, SPO_2 were monitored at regular intervals throughout the procedure and all the patients were monitored continuously to combat with any adverse effects immediately. TPE was performed daily in these patients till clinical improvement was noted in the form of decrease in symptoms and improved urinary output and lab parameters.

Statistical analysis

All data are entered into the SPSS V20. Continuous data are expressed as mean ± SD. The data which follows non -parametric distribution, Wilcoxon Signed Rank test is applied for calculation of probability value.

p-value ≤0.05 considered to be statistically significant difference.

RESULTS

Fifteen children (10 male, 5 female) with mean age, 7 ± 2.13 (range: 4-11) years, mean body weight, 18.82 ± 4.42 kg were subjected to 119 TPE procedures in all, with mean TPE of 7.9 (range: 2-18) per patient. Mean plasma volume processed was 3308.5 ± 6466.69 ml, average plasma removed was 1048.06 ± 445.98 ml, average fluid replaced was 839.23 ± 428.35 ml and average duration of the procedure was 43.36 ± 14.3 minutes. (Table 1) Six patients had blood group B positive (+ve), 4 patients were A +ve and 5 were O +ve. Hemoglobin of two patients, one with blood group O +ve and one with B +ve was < 5 gm/dL.

No serious adverse effect was encountered during/ after TPE in any patient. One patient developed rash during patient's last TPE (4^{th}) at the end of the procedure, due to allergens in the FFP which was treated with intravenous Chlorpheniramine maleate 25 mg and Hydrocortisone 100 mg. Three patients had poor access flow during

the procedure. Flushing with NS helped in recovering flow. There were no machine errors during any of the procedures. The post procedure course was uneventful in all.

Average pre and post TPE platelet count was 96.53 ± 75.33 x 10^9/L and 116.80 ± 80.30 x 10^9/L(p value 0.34)Average pre and post TPE hemoglobin was 6.76 ± 1.79 gm/dL and 8.13 ± 2.12 gm/dL(p value 0.05). Average pre TPE and post TPE serum creatinine was 1.434 ± 1.84 and 0.728 ± 0.62 mg/dl (p value<0.01) (Table 2)

In 10 (66.7%) patients platelet count showed improvement at the time of last exchange as compared to the count before the first TPE. In 5 (33.3 %) patients platelet count showed decline. However 3 patients out of these 5 showed gradual improvement in platelet count and the count was normalized at the time of last follow up. The platelet count increased from 87 x 10^9/L to 2.48 x 10^9/L at 31 days in 1 patient, from 15 x 10^9/L to 241 x 10^9/L at 108 days in second, and from 198 x 10^9/L to 499 x 10^9/L at 105 days in the third patient. Twelve patients showed improved hemoglobin level at the end of last exchange, however 3 patients with improving platelet count showed decreased hemoglobin at the end of last TPE. Two out of these 3 patients showed improved hemoglobin (gm/dl) from 8 to 14.3 at 51 days and 5 to 7.7 at the end of 55 days. One patient was lost to follow up. There is a statistically significant improvement in the serum creatinine and hematocrit level but not that significant improvement in the platelet count. There is no correlation between number of exchanges and improvement in the laboratory parameters.(Figure 1)

DISCUSSION

TPE is the first line of treatment for aHUS. This study was conducted to assess the safety and efficacy of TPE in aHUS. All the patients showed improvement in their clinical condition after TPE. None of the patients showed any serious adverse effect during the procedure except for the allergic reaction to FFP. In a retrospective study for 13 years conducted in north India by Hans et al on 26 aHUS patients, overall response rate of 87.5% and survival rate of 80% was observed. We observed a 100% response rate. The most common complication observed by them was allergic reaction to FFP which is similar to our study. However we did not evaluate the time between the onset of illness and initiation of therapy. Hans et al concluded that sooner the therapy is started better is the response. In our study the therapy was continued till clinical response was obtained as cost was not a deterrent. In Gujarat since children are covered under school health program all the patients could continue the therapy till clinical improvement was observed. This could be the reason why all the patients showed improvement. In our study a mean of 7.9 procedures were performed per patient which is similar to their study .[8] There is a significant improvement in creatinine levels and hemoglobin but not that significant improvement in platelet count.TPE can be performed safely in pediatric patients which is an observation similar to the study conducted by Gajjar M, Patel T et al in patients of GBS.[9] In addition to the estimation of anti-factor H antibodies genetic analysis of complement factors should also be done.[10] However since estimation of anti factor H is costly and it is done in very selected laboratories in India its estimation was not repeated after TPE. Eculizumab an anti C5 monoclonal antibody inhibitor of the complement pathway is the recommended first line of treatment in aHUS.[11] In very young pediatric patients Eculizumab should be the first line of treatment.[12] However because of its unavailability and high cost in India TPE is gold standard and safe for the treatment of aHUS in pediatric patients in India. TPE is beneficial in aHUS. [13-15]

Limitations of the study:

Genetic analysis was not available in our setting and hence we could not perform it. The duration between TPE and clinical diagnosis is not mentioned due to non-availability of data.

Anti factor H was not repeated after TPE.

CONCLUSION

Thus, TPE is a safe therapeutic maneuver and an adjuvant in the treatment for aHUS in India, which otherwise progresses to chronic renal failure in pediatric patients.

Abbreviations

a HUS: Atypical Hemolytic Syndrome
L: Liters
MAHA: Microangiopathic Hemolytic anemia
PCV: Packed Cell Volume
TPE: Therapeutic Plasma Exchange

ACKNOWLEDGEMENTS:

We are grateful to I/C Director, Dr. Vineet Mishra and members of the Academic Council, IKDRC, for granting permission to publish the data of this observational study. Our Physician colleagues from the department of Nephrology and Pediatric Nephrology and Transplant Medicine, nursing staff and all lab staff deserve special thanks for their respective role in testing, thereby providing support in completing this work successfully. The authors acknowledge the contribution of the treating Paediatric Nephrologists, Biostatistician and all the staff members working in department of Pathology, Lab Medicine and Blood bank.

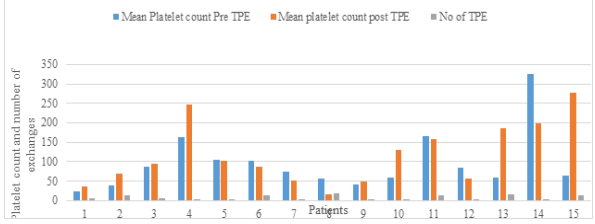
Table 1 Mean Data of TPE procedures

Patient	Weight Kg	Volume Processed (ml)	Plasma Removed (ml)	Fluid Replaced (ml)	Duration (minutes)	Number Of Exchanges Performed
1	13.85	1219	678	476	50.8	5
2	26.46	2704	1685.29	1406.4	57	13
3	20.84	26575.5	1642.16	1436.6	61	6
4	16.2	1648	1067	903.25	48.25	4
5	20.6	2059	1410	1246	46	4
6	23.9	3285	2025	1799	70.8	12
7	14.73	1108	708	478.6	39.33	03
8	14.59	993.11	521.94	360.22	22.38	18
9	11.12	1300	559	512.5	55.75	04
10	22.33	1172.6	816.5	633.3	33.3	04
11	22.46	1614.84	1021.46	636.76	21	13
12	17	1194.5	772.5	638	26.5	02
13	23.06	1559.8	909.6	663.86	37.6	15
14	19.5	1600.2	910.25	638	41.70	04
15	15.75	1594.58	994.3	760.08	43.08	12

Table 2 Results

	Platelet count X109/l		Hemoglobin gm/dl		Serum Creatinine mg/dl	
	Pre TPE	Post TPE	Pre TPE	Post TPE	Pre TPE	Post TPE
1	23	35	7.5	8.2	0.55	0.45
2	39	69	10.6	8	0.51	0.47
3	87	94	6	7.3	0.73	0.6
4	164	247	7.7	5	0.58	0.51
5	104	110	5.2	6.9	5.26	2.9
6	102	100	5.9	7.7	6.49	0.51
7	75	50	4.1	7	0.98	0.55
8	55	65	5.1	8.8	1.67	0.93
9	42	48	8	10.5	0.4	0.32
10	59	130	6.5	6.7	0.68	0.5
11	165	159	9.6	8.4	0.99	0.72
12	84	55	4.7	4.9	0.8	0.6
13	59	186	6.8	12.1	0.44	0.39
14	325	300	6.1	12	0.98	0.81
15	65	278	7.6	8.5	0.46	0.31

Figure 1 Comparison between platelet count and number of exchanges performed.



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