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# Therapeutic plasma exchange in HELLP syndrome: A life savior

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## Abstract:

**BACKGROUND:** HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome occurs in about 0.5%–0.9% of all pregnancies, but its prevalence is higher in patients with severe preeclampsia, accounting for a substantial maternal and perinatal morbidity and mortality. According to the latest American Society for Apheresis guidelines, Therapeutic plasma exchange (TPE) performed for postpartum cases and antepartum HELLP syndrome cases fall in Categories III and IV, respectively.

**MATERIALS AND METHODS:** Retrospective analysis was done at our tertiary care center from January 2014 to June 2019 for patients diagnosed with HELLP syndrome. Clinical data for age, gestational age at the time of diagnosis, type of delivery, outcome of pregnancy, history of preeclampsia / eclampsia, hemoglobin levels, AST, ALT, LDH, platelet counts, prothrombin time, activated partial thromboplastin time, international normalised ratio, complete blood count, was obtained from patients' electronic medical records. The TPE was initiated within 24 hrs of diagnosis. All TPE was done on Spectra Optia apheresis system (Terumo BCT, Inc, USA). Statistical testing was conducted with the statistical package for the social science system version SPSS 20.0 and R-3.2.0. Continuous variables were expressed as mean $\pm$ SD and were compared between Pre and Post TPE records of patients by using the paired *T* test.

**RESULTS:** Nine patients fulfilled the criteria of HELLP syndrome. Seven (77.8%) were diagnosed in the postpartum period and 2 (22.2%) during the second trimester. Out of the total nine patients, two patients (22.2%) recovered completely and were discharged on day 15  $\pm$  7 days, whereas 4 (44.4%) patients were discharged on day 21  $\pm$  7 days with the advice of hemodialysis. Two (22.2%) patients had an intrauterine death and were discharged 3–4 days after the demise. In all these patients (except one), the TPE was initiated within 24 h of the diagnosis. A significant increase in platelet count and decrease in the lactate dehydrogenase levels ( $P < 0.05$ ) was observed post TPE.

**CONCLUSION:** Our data showed that TPE improved the treatment outcome in patients with HELLP syndrome despite being a Category III and IV indication among postpartum and antenatal females, respectively. However, a timely diagnosis and management are of paramount importance for a favorable outcome. TPE needs to be performed within 24 h of the diagnosis postdelivery when the patient is not responsive to the usual therapies, especially in class I HELLP syndrome.

## Keywords:

American Society for Apheresis, elevated liver enzymes, hemolysis, low platelet count, therapeutic plasma exchange

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## Introduction

The HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome is a serious complication associated with pregnancy. It was described as a severe form of preeclampsia in 1982 by Weinstein,<sup>[1]</sup>

but later found to be prevalent in 10%–20% of cases with preeclampsia.<sup>[2]</sup> HELLP syndrome is characterized by the triad of hemolysis, elevated liver enzymes, and low platelet counts (PC). There exists a partial or incomplete form of the disease which includes one or two parts of the triad.<sup>[2]</sup>

HELLP syndrome occurs in about 0.5%–0.9% of all pregnancies, but its prevalence is

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higher in patients with severe preeclampsia, accounting for a substantial maternal and perinatal morbidity and mortality.<sup>[2,3]</sup> HELLP syndrome usually begins during the third trimester with the peak frequency between the 27<sup>th</sup> and 37<sup>th</sup> gestational weeks.<sup>[2]</sup> It can also occur within 48 h postpartum, wherein it is associated with disseminated intravascular coagulation (DIC).<sup>[4]</sup>

The laboratory findings include microangiopathic hemolysis with fragmented red cells and polychromasia on the peripheral blood smear, liver function abnormalities, thrombocytopenia (PC <100 × 10<sup>3</sup>/μL), increased serum lactate dehydrogenase (LDH), increased serum aspartate aminotransferase (AST), and alanine aminotransferase (ALT).<sup>[5]</sup> Along with LDH, which reflects both the extent of hemolysis and hepatic dysfunction, the PC is used for investigating the disease progression.<sup>[2]</sup> The most severe morbidity and mortality associated with HELLP syndrome are observed when the PC is reduced below 50 × 10<sup>3</sup>/μl.<sup>[6,7]</sup>

Delivery remains the definitive treatment for antenatal HELLP. A conclusive role of therapeutic plasma exchange (TPE) in this condition has not been established. However, nonresponsive postpartum HELLP, TPE is a Category III indication.<sup>[8]</sup> TPE can replace a patient's plasma with donor plasma and remove pathological substances in the bloodstream. It replaces the coagulating factors, albumin, and biologically active substances that normally are produced by the liver cells. TPE also removes ammonia, endotoxins, bilirubin, and inflammatory cytokines from the circulation.<sup>[9]</sup> Transfusing large volumes of fresh frozen plasma (FFP) helps to restore the coagulation parameters which improves the DIC. Renal functions are improved consequently with the removal of vasoactive factors like renin and angiotensin. This improves the overall hepatic, renal and neurological functions in patients with HELLP syndrome.<sup>[10,11]</sup> We present here a study of 9 HELLP syndrome cases wherein TPE was used as one of the modalities for treatment.

## Materials and Methods

A retrospective analysis was performed at our tertiary care center from January 2014 to June 2019 for patients diagnosed with HELLP syndrome where TPE was performed. Relevant clinical data were obtained from patients' electronic medical records maintained by the hospital. HELLP syndrome was defined by the presence of all three criteria, namely hemolysis (LDH >600 U/L, increased serum bilirubin, presence of schistocytes in peripheral smear), elevated liver enzyme (AST >70 U/L), and low (PC <150000/μl). Patients were diagnosed and classified with HELLP syndrome as per the Mississippi-Triple Class System<sup>[2]</sup> [Table 1].

All patients were admitted to the intensive care unit of the hospital and data was collected until the clinical and lab evidence of HELLP showed improvement as per the records. The patients' characteristics including age, gestational age at the time of diagnosis, type of delivery, the outcome of pregnancy, history of preeclampsia/eclampsia, hemoglobin levels (Hb) levels, AST, ALT, LDH, PC, prothrombin time (PT), activated partial thromboplastin time (APTT), international normalized ratio was noted before the start of TPE and after every exchange. The complete blood count was performed on a Beckman Coulter analyzer (Beckman Coulter, California, USA) device using the impedance method. PC was confirmed by peripheral smear in each patient.

The American Society for Apheresis (ASFA) guidelines were referred from time to time for management, treatment, and assessing the rationale for therapeutic apheresis.<sup>[8,12,13]</sup> A central venous catheter was placed and the TPE was performed for patients unresponsive to delivery, steroid or supportive therapy (blood and blood components, anti-hypertensives, and antibiotics). The TPE was initiated preferably within 24 h of diagnosis upon receiving the request from the treating physician as a prophylactic measure. All TPE was done on Spectra Optiaapheresis system (Terumo BCT, Inc, USA) which has a fully automated mode of operation. TPE was performed in the postpartum HELLP until the PC was >100 × 10<sup>9</sup> or LDH was normalized.<sup>[8]</sup>

Statistical testing was conducted with the Statistical Package for the Social Science system version SPSS 20.0 and R-3.2.0. Continuous variables were expressed as mean ± standard deviation and were compared between Pre- and Post-TPE records of patients by using the paired *t*-test. All "p" values were two-tailed with significance defined as *P* < 0.05 at the level of 95% confidence limit.

## Results

Nine patients fulfilled the criteria of HELLP syndrome. Seven (77.8%) were diagnosed in the postpartum period and 2 (22.2%) during the second trimester. Among these patients (*n* = 9), 8 (88.9%) were Class I and 1 (11.1%) was Class II, according to The Mississippi-Triple Class System [Table 1]. The clinical profile of the patients is described in Table 2. The patients received 10 mg doses of dexamethasone intravenously every 12 h until delivery and 3 additional doses after delivery.

The average number of TPE required per patient was 4 procedures. An average of 1.5 plasma volumes was processed per procedure per patient. The procedures were

**Table 1: Patient classification as per the (citation)-Triple Class System**

HELLP class <sup>[2]</sup>	Number of patients (n)
Class I (PC<50×10 <sup>9</sup> , AST/ALT ≥ 70 U/L, LDH>600 U/L)	8
Class II (PC 50-100×10 <sup>9</sup> , AST/ALT ≥ 70 U/L, LDH>600 U/L)	1
Class III (PC 100-150×10 <sup>9</sup> , AST/ALT ≥ 40 U/L, LDH>600 U/L)	0
Total	9

HELLP=Hemolysis, Elevated Liver enzymes, Low Platelet count, PC=Platelet counts, AST=Aspartate aminotransferase, ALT=Alanine aminotransferase, LDH: Lactate dehydrogenase

**Table 2: Clinical profile of patients/reported cases**

Features	Condition	Number of cases, n (%)	Total (n)
Mean gestational age	34±3 weeks	9	9
Time of diagnosis	Postpartum	7 (77.8)	9
	Antipartum	2 (22.2)	
Parity	Primigravida	7 (77.8)	9
	Multigravida	2 (22.2)	
Missisipi score	Missisipi score I	8 (88.9)	9
	Missisipi score-II	1 (11.1)	
	Missisipi score-III	0	
History of preeclampsia or eclampsia	Eclampsia	2 (22.2)	9
	Preeclampsia	7 (77.8)	
Mode of delivery	Caeserian	8 (88.9)	9
	Normal vaginal delivery	1 (11.1)	

performed daily with FFP as replacement fluid. The replacement of the fluid was kept at 100% to maintain the patient in a euvolemic state. Three ampoules of injection calcium gluconate 10% diluted in normal saline was administered as a prophylaxis for Acid Citrate Dextrose (ACD) induced hypocalcemia. The procedures were well tolerated and there was no serious complication to the patient during or after the procedure.

Out of the total nine patients, two patients (22.2%) recovered completely and were discharged on day 15 ± 7 days, whereas 4 (44.4%) patients were discharged on day 21 ± 7 days with the advice of hemodialysis due to persisting kidney injury. Two (22.2%) patients had an intrauterine death and were discharged 3–4 days after the demise. In all these patients, the TPE was initiated within 24 h of the diagnosis. One patient (11.1%) was referred from a primary health-care center of a two-tier city and could be attended only after a week. Only one plasma exchange could be performed on this patient after the elective Lower Segment Caesarean section (LSCS). She later succumbed to acute renal failure and DIC.

Laboratory profile during pre- and post-TPE sessions, including Hb, APTT, LDH, AST, ALT, total bilirubin, PT, and APTT parameters showed an improvement in all the patients [Table 3] with a significant increase in PC and decrease in the LDH levels ( $P < 0.05$ ) postTPE. There was also a nonsignificant improvement in Hb levels and liver enzymes postTPE.

## Discussion

HELLP syndrome is a progressive disorder that affects many systems in the body, significantly contributing to perinatal morbidity and mortality.<sup>[10,11]</sup> In HELLP syndrome, several complications leading to therapeutic management, timing, and method of delivery may arise impacting the health of the mother and fetus. The clinical manifestation of HELLP syndrome includes thrombocytopenia, hemolysis, and liver dysfunction. Other clinical entities that can present with similar microangiopathic features include immune thrombocytopenia, thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome, antiphospholipid antibody syndrome, systemic lupus erythematosus, acute fatty liver of pregnancy, and HELLP like conditions caused by severe hypovolemic shock, sepsis and sickle cell crisis.<sup>[8]</sup>

Maternal mortality is high in patients of HELLP syndrome, especially those belonging to Class I. The mortality rate ranges from 1% to 25% and is dependent on class, delayed diagnosis, presence of infection, and acute renal failure.<sup>[10]</sup> In our study, out of nine patients, six patients were discharged, with no maternal or fetal morbidity. Similar findings were reported by Simetka *et al.*<sup>[14]</sup> Martin *et al.* found a maternal mortality rate of 3.2% in their 62 patients with HELLP syndrome.<sup>[10,15]</sup> Renal failure is the most important cause of mortality in HELLP syndrome. Studies have reported a renal failure rate of 1.2% in patients previously.<sup>[15]</sup> In this study, the only patient that succumbed developed renal failure and could not be revived. However, the patient was brought to us almost a week after the LSCS and the TPE could be initiated only after that. This explains the need for prompt diagnosis and initiation of therapy at the earliest.

The definitive treatment for HELLP syndrome is an urgent delivery by cesarean section. In our study, out of nine patients, 8 were delivered through cesarean section. Prolongation of pregnancy has been associated with an increase in maternal mortality. According to the latest ASFA guidelines, TPE performed for postpartum cases and antepartum HELLP syndrome cases fall in Categories III and IV, respectively.<sup>[8]</sup>

**Table 3: Pre- and post-plasma exchange pattern of laboratory profile of patients**

Parameters	Mean±SD		P	Normal range
	Preplasma exchange	Postplasma exchange		
Hb (g/dl)	7.75±1.16	9.24±0.49	0.936	11-15
Platelet (per mm <sup>3</sup> )	40,833.33±31,211.64	107,776.59±50,216.14	0.03	150-410
LDH (U/L)	4886±10,008.1	1705.22±951.37	0.04	140-280
AST (U/L)	292.33±411.12	100.17±117.88	0.229	<34.0
ALT (U/L)	337±627.67	49.24±51	0.298	10-49
Total bilirubin (mg/dl)	5.28±5.41	2.04±1.44	0.378	0.3-1.2
APTT (s)	27.87±14.78	23.93±12.2	0.376	26.4-36.8
INR	1.16±0.23	1.04±0.05	0.677	<1.1
Creatinine (mg/dl)	3.78±1.39	3.52±0.99	0.936	0.6-1.1

Hb=Hemoglobin, LDH: Lactate dehydrogenase, AST=Aspartate aminotransferase, ALT=Alanine aminotransferase, APTT=Activated partial thromboplastin time, INR=International Normalized Ratio, SD=Standard deviation

TPE is an effective treatment modality in HELLP, especially in the management of thrombocytopenia, and nonresponsiveness to conservative therapy. In these patients, TPE removes circulatory protein-bound platelet aggregating and procoagulant factors released from the activated platelets and endothelial cells. This improves the clinical condition of the patient along with an increase in the PC, hematocrit and decrease in the serum LDH levels. A significantly elevated level of LDH is used as a marker of hemolysis. Dave *et al.* investigated the role of LDH in association with adverse effects in preeclampsia and eclamptic cases.<sup>[16]</sup> In our patients, there was a significant improvement in both these parameters. The other parameters including the blood counts and biochemical parameters also improved, although not significantly. Our results corroborate with previous studies.<sup>[6,9-11,15]</sup> In a study by Bayraktaroglu *et al.*, thirteen patients with HELLP syndrome were treated with one or two sessions of TPE after delivery. Rapid improvement in PC was observed after treatment with TPE.<sup>[17]</sup> Simetka *et al.*, observed in their retrospective analysis, 81 patients showed improvement in PC and LDH values at 72 h postpartum and for bilirubin in 24–48 h.<sup>[14]</sup> Trends for AST and PC differed significantly between the recovery and progression groups in the 1<sup>st</sup> 48 h.<sup>[14]</sup> The marked improvement in Hb level and PC may be due to the shortening of the thrombotic process and inactivation of platelets in HELLP patients, as suggested in previous studies.<sup>[9]</sup>

TPE is generally done 48–72 h after the delivery if there is a failure of the patient to improve. However, there are reports which suggest that TPE done within 24 h have been reported to dramatically improve the patient outcome and reduces the mortality rate in class I HELLP.<sup>[9,10]</sup> Eser *et al.* investigated the effects of early postpartum use of TPE in patients with HELLP syndrome on outcomes.<sup>[9]</sup> The study reported a reduced mortality rate, length of stay, and recovery times in TPE-treated patients with HELLP syndrome as compared with the control group. In addition, a rapid improvement in PC,

ALT, LDH levels was observed.<sup>[6]</sup> This study reported that postpartum, early TPE therapy improves clinical outcomes in patients with severe HELLP syndrome.<sup>[6]</sup> Usually, it is found that during the postpartum period, the majority of cases showed resolution of the disease within 72 h of delivery. However, some patients, especially those with the persistent form of the disease do not improve or even become worse. To prevent further worsening, TPE is done in the postpartum period. We initiated TPE in all the patients within 24 h of establishing the diagnosis postdelivery prophylactically considering these reports.<sup>[9,10]</sup>

TPE is a choice for treatment in HELLP and significantly improves the outcome in patients refractory to conservative steroid therapy as supported by previous studies.<sup>[2,4,18]</sup> In our study, all the patients were refractory to steroids. TPE along with glucocorticoids showed improvement in these cases. In a prospective, double-blind clinical trial study, by Fonseca *et al.* including 132 women with HELLP syndrome.<sup>[19]</sup> The patients received 10 mg doses of dexamethasone intravenously every 12 h until delivery and 3 additional doses after delivery and found that the use of dexamethasone for the treatment of HELLP syndrome was not effective.<sup>[20]</sup> Similarly, steroids were started along with prophylactic TPE in our cases to mitigate the risks and aimed to receive better results.

Thrombocytopenia is mainly used to classify the severity of HELLP syndrome in the Mississippi-Triple Class System. Class, I patients have higher mortality than other patients.<sup>[15]</sup> Our study included patients of both Class I and II, however, the majority of the patients were of a Class I HELLP syndrome, who deteriorated despite completion of delivery and hence needed TPE and other supportive therapies.

There were few limitations in our study. First, ADAMTS 13 investigation could not be performed due to technical insufficiency, which could have distinguished these patients from TTP where TPE is the primary therapy.



Nonetheless, the role of TPE is instrumental in these patients. Second, there was no control group in the study. Our study was done in only nine patients and the majority of them were postpartum cases.

## Conclusion

Our data showed that TPE improved the treatment outcome in patients with HELLP syndrome despite being a Category III and IV indication among postpartum and antenatal females, respectively. However, a timely diagnosis and management are of paramount importance for a favorable outcome.

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## Conflicts of interest

There are no conflicts of interest.

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