Role of plasma exchange in management of patients clinically diagnosed of postpartum thrombotic microangiopathies: A retrospective observation from a tertiary health-care center

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Abstract:
INTRODUCTION: Diagnosis of postpartum thrombotic microangiopathies in pregnancy is a challenge, but plasma exchange (PE) is life-saving in such cases. This study was conducted with the aim to find the result of the early start of PE in such patients.

MATERIALS AND METHODS: There were a total of seven clinically diagnosed cases of postpartum thrombotic microangiopathies (PP-TMA) where PE was done. The diagnosis of PP-HUS and decision to start PE in such cases were based on the classical triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. All the PE procedures were done using fully automatic COM.TEC (Fresenius Kabi, Germany).

RESULTS: Immediately before the start of PE, the mean platelet count and serum lactate dehydrogenase (LDH) and hemoglobin (Hb) were 53.1 × 10⁹/L, 10,943 IU/L, and 6.4 gm%, respectively. After seven sessions of PE, platelet count improved to 158 × 10⁹/L and LDH dropped to 609 IU/L, and Hb improved to 10.3 gm% (P < 0.05). We got a positive renal response in four patients in whom serum creatinine value reached within normal range while in the remaining three patients, no positive renal response was obtained and serum creatinine remained above normal range. Thus, the response of PE was shown to be inadequate in three patients. Compliance to PE was good. Patients were discharged after 20 days (mean) of hospital admission.

CONCLUSION: PE is life-saving in PP-HUS. High degree of clinical suspicion to it and early start of PE were crucial for successful outcome in our patient population.

Keywords:
Microangiopathic hemolytic anemia, postpartum thrombotic microangiopathies, schistocytes, therapeutic plasma exchange, thrombocytopenia

Introduction

Thrombotic microangiopathies (TMAs) are clinical disorders characterized by abnormal coagulation and microvascular thrombosis. TMAs are uncommon but life-threatening disorders in pregnancy. TMAs are classically characterized by thrombocytopenia, microangiopathic hemolytic anemia (MAHA), and microvascular thrombosis.¹

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thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are two well-established forms of TMAs which are extremely difficult to differentiate. Although there are no distinguished criteria to differentiate TTP from HUS, it is said that patients with TTP predominantly present with neurological abnormalities while patients with HUS present with renal abnormalities (along with thrombocytopenia and MAHA). TTP usually presents during early pregnancy while HUS occurs during the term or postpartum. However, there are no distinguished criteria to differentiate these two clinical syndromes during pregnancy. The definitive diagnosis of TTP is established with the measurement of ADAMTS 13 activity whereas the diagnosis of postpartum atypical HUS (aHUS) is established with complement factor mutation analysis. In Indian scenario, the distinction between TTP and HUS is next to impossible because either the tests are not available or its time-consuming. Thus, in the present study, the diagnosis of postpartum TMAs is mainly clinical, and further course of action is mainly dependent on clinical diagnosis. Based on published literature, the role of plasma exchange (PE) has been found to be phenomenal in case of TTP where it has reduced the mortality to <10%. The role of PE in postpartum aHUS is highly debatable. Egerman et al. and others have emphasized that improved survival in PP-HUS is attributed to aggressive treatment with PE. However, some of the recently published data have not shown the significant response of PE in pregnancy-associated aHUS. In our cases, since we were not able to differentiate TTP from HUS, we used postpartum TMAs as a common terminology. The aim of the present retrospective study was to find the effect of PE in seven clinically diagnosed cases of TMAs.

Materials and Methods

Settings
This retrospective observational study was conducted at the department of transfusion medicine in a tertiary health-care center in the National Capital Region of India. Between June 2015 and December 2017 (31 months), there were a total of seven cases where the clinical diagnosis of postpartum TMAs was established, and PE was started. All the cases were from various maternity and nursing homes that were referred to our hospital for the management of postpartum thrombocytopenia and deteriorating kidney function. The diagnosis of post partum thrombotic microangiopathies (PP-TMA) and decision to start PE in such cases were based on the classical triad of MAHA, thrombocytopenia, and acute renal failure. For the diagnosis, we took in to account the patient’s clinical presentation, systems involved and the severity of disease.

Hematological and biochemical parameters
Hematological parameters (hemoglobin% [Hb], TLC, hematocrit%, and platelet count) were measured on XN 1000 hematology analyzer (Sysmex, USA). Peripheral blood smear was seen and reported by an expert hematopathologist. Biochemical parameters such as serum lactate dehydrogenase (LDH) and kidney function tests were done on Vitros 5600 (Ortho-Clinical Diagnostics, USA). All the procedures were done as per the department standard operating procedures and manufacturer’s instructions. To see the effectiveness of PE, hematological, and biochemical parameters (Hb%, LDH, and platelet count) were measured after every alternate procedure.

Therapeutic plasma exchange
All the PE procedures were done using fully automatic COM.TEC ( Fresenius Kabi, Germany). One standard PE procedure was 1.5 plasma volume exchange using fresh frozen plasma as replacement fluid. Patient’s informed consent was obtained before each procedure. All the procedures were done on the double lumen femoral dialysis catheter under complete aseptic precautions. If a patient experienced any adverse reaction/complication during PE procedure, they were managed accordingly. Prophylactic administration of calcium gluconate (one ampoule diluted in 100 ml of 0.9% normal saline) was done for every 1000 ml of plasma removed. Patient who had allergic reaction during the last procedure was given prophylactic intravenous injection Avil before the start of next procedures. Seven sessions of PE were done on daily basis. If the response to PE was as per the definition, no further procedures were done while if not so, couple of more procedures were done on an alternate day and response was noted. No further procedures were done if no adequate response was noticed.

Definition of response to plasma exchange
For the definition of response to PE, we took reference of published literature and modified it a bit according to our study. The three important parameters to measure the effectiveness of PE were (1) platelet count, (2) serum LDH, and (3) serum creatinine after every alternate session of PE. Response to PE was considered adequate if all the three parameters reached within normal range after the required number of PE procedures. Response to PE was considered inadequate if it did not fulfill all or any of the three criteria. Those patients who gave adequate response were further followed to see the status of remission and relapse. Remission was defined when PE was not repeated within 30 days of completion of the last procedure. Relapse was defined as recurrence of symptom and restart of PE procedures after remission. The definition of remission and relapse was not applicable in patients who did not give adequate response to PE.

For the response to PE, the two other subjective parameters, we took into the consideration were the improvement in patient’s clinical condition and rising Hb.
Data collection and analysis

For each procedure patients’ demographic data, laboratory investigations, and PE details were maintained on an excel sheet. Patient’s clinical data were obtained from her file and hospital information system. Data were further analyzed using the statistical package for the social sciences version 21 (SPSS, Chicago, IL, USA). The effectiveness of PE was measured considering preprocedure value as the baseline (value just before the start of the 1st PE procedure). Three parameters—platelet count, serum LDH, and serum creatinine were taken into consideration for the measurement of the effectiveness of PE. Normality of data distribution was done using Shapiro–Wilks test at 5% level of significance. P > 0.05 showed normal distribution of data. For checking the significance of difference, paired t-test was done for normally distributed data, and Wilcoxon-rank test was done for nonnormal data. P < 0.05 was considered statistically significant.

Results

During the period of observation, there were a total of seven cases in which the clinical diagnosis of postpartum TMA was made, and PE was done. Among the seven patients, four had gravida 1 (G1P1A0) while three had gravida 2 (G2P1A1). Two patients had normal vaginal delivery while five had cesarean section. All were full-term pregnancies. The mean age of patients was 28 (range 20–34). None of the patients had a history of hypertension, edema, and proteinuria (suggestive of preeclampsia) during the antenatal period. Two to 5 days after the delivery patients started complaining of abdominal heaviness/pain, disorientation, vomiting, dyspnea, and drastic decrease in urine out. Four patients presented with fever as the first clinical presentation while the remaining three patients presented with abdominal pain and decreased urine output as the 1st primary chief presentation. In none of the cases, there was a spontaneous recovery.

At the time of admission, laboratory investigations, such as mean Hb, PC, LDH, and S. creatinine, were 6.4 gm%, 53.1 × 10⁹/L, 10943 IU/L, and 4.2 mg/dl, respectively. In all seven patients, peripheral blood smear showed the presence of polychromasia, schistocytes, and nucleated red blood cells. Thus, the three features which were common in all patients were thrombocytopenia, MAHA, and acute renal abnormalities. Four patients had couple of sessions of hemodialysis before the start of PE while in remaining three, PE was started first. PE procedures were started on the 8th day of delivery (range, 6–10 days) and within 2 days of admission to our hospital. In our patient population, the median number of PE procedures done were seven (range = 7–9) [Table 1]. All the procedures were done aggressively on daily basis. Response to PE in terms of improvement in laboratory parameters such as Hb, PC, LHD, S. creatinine, and other parameters are shown in Table 2. The sequential change in these 4 parameters (platelet count, LDH, s.creatinine and Hb) has been shown in Figures 1-4. Immediately before the start of PE, the mean platelet count and serum LDH and Hb were 53.1 × 10⁹/L, 10943 IU/L, and 6.4 gm%, respectively. After the required number of PE sessions, platelet count improved to 158 × 10⁹/L and LDH dropped to 609 IU/L, and Hb improved to 10.3 gm% (P < 0.05). We got a positive renal response in four patients in whom serum creatinine value reached within normal range while in the remaining three patients no positive renal response was obtained and serum creatinine remained above normal range. Thus, the response of PE was shown to be inadequate in three patients. That’s the reason why Table 2 demonstrates nonsignificant (P > 0.05) drop in serum creatinine and other renal parameters after PE sessions.

The patients who gave an adequate response to PE demonstrated the state of remission with further significant improvement in laboratory and clinical parameters and none of the patients relapsed till now [Table 2]. In patients who gave an inadequate response to PE became dialysis dependent and till now none of the patients have undergone renal transplantation.

We did not observe any mortality during PE and compliance to PE was good in all but one, where the patient developed urticaria and mild hypotension just before the end of one session which was managed conservatively. No other complications were observed during and after the PE procedures. Patients required 20 days of admission (15–27 days) to our hospital [Table 1].

Discussion

Thrombotic microangiopathy in pregnancy is a rare event with the incidence of 1 in 25,000 pregnancies.[11] It is classically characterized with MAHA, thrombocytopenia, and predominantly with acute renal abnormalities. Making a diagnosis of postpartum aHUS is a challenge for clinicians. On the one hand, it needs to be differentiated from TTP, while on the other hand, it needs to be differentiated from other more common pregnancy-related syndromes. To be more precise acquired or constitutional deficiency in ADAMTS 13 causes TTP while lack of control of the alternative C3 convertase has been established as a risk factor for the occurrence of pregnancy-associated aHUS. Dysregulation of complement could be acquired (anti-FH antibodies) or constitutional (mutation in factor H, factor I, factor B, membrane cofactor protein-coding genes, and C3 coding genes).[11‑13] In spite of knowing the diagnostic utility of ADAMTS 13 enzyme activity assay and/or
| Patients | Age (years) | Symptoms and signs | Hb/Hct | PC | LDH | Schistocytes (yes/no) | Day of start of PE from delivery | Number of dialysis before PE | Compliance to PE (good/poor) | Complications during PE | PC/LHD after 7 PE | Total number of PE procedures | LOS |
|----------|-------------|--------------------|--------|----|------|----------------------|-------------------------------|-----------------------------|-----------------------------|--------------------------|----------------|-----------------------------|------|
| 1        | 25          | Fever, confusion, disorientation, abdominal pain, vomiting, decreased urine output | 6.9    | 45 | 2.1  | 12000 | Yes                  | 8                             | 0                           | 2 | Good                      | None          | 160/585                      | 7    | 15  |
| 2**      | 31          | Fever, vomiting, no urine output, bleeding from surgical site | 5.1    | 40 | 2.8  | 21000 | Yes                  | 10                           | 2                           | 2 | Good                      | None          | 129/2424                     | 9    | 27  |
| 3        | 28          | Dyspnea, vomiting, abdominal pain, no urine output | 6.9    | 121 | 6.5  | 9000  | Yes                  | 7                            | 1                           | 2 | Good                      | Urticaria, mild hypotension | 158/480                      | 7    | 17  |
| 4**      | 20          | Fever, seizure, abdominal pain, bleeding from surgical site, decreased urine output | 7.8    | 21 | 2.6  | 15000 | Yes                  | 9                            | 2                           | 0 | Good                      | None          | 136/1350                     | 9    | 23  |
| 5        | 34          | Dyspnea, abdominal pain, vomiting, decreased urine output | 6.1    | 40 | 3.1  | 8000  | Yes                  | 7                            | 2                           | 0 | Good                      | None          | 170/600                      | 7    | 19  |
| 6        | 30          | Disorientation, hematuria, decreased urine output, abdominal pain, nausea | 6.2    | 60 | 3.3  | 4000  | Yes                  | 6                            | 1                           | 0 | Good                      | None          | 170/521                      | 7    | 18  |
| 7        | 28          | Fever, decreased urine output, abdominal pain, vomiting, bleeding from the surgical site | 5.5    | 45 | 3.4  | 7600  | Yes                  | 8                            | 2                           | 2 | Good                      | None          | 152/565                      | 7    | 22  |

*In case 2 and case 4 additional two procedures were required for the adequate response to PE. LOS=Length of hospital stay, Hb=Hemoglobin, HCT=Hematocrit, LDH=Lactate dehydrogenase, PE=Plasma exchange, PC=Platelet counts.
complement factor mutation analysis in the definitive diagnosis of HUS, it was not done in our patients because of long turnaround time for ADAMTS 13 enzyme activity assay and nonavailability of complement factors mutation analysis. PE was started as soon as the clinical diagnosis of postpartum TMA was established. In the present study, all patients where postpartum TMAs was diagnosed, and PE was done were having (1) thrombocytopenia, (2) MAHA (abnormally high LDH and fragmented red cells in peripheral blood smear), and (3) acute renal abnormality. Rest other prominent supportive findings were: (1) severity of clinical presentations at the time of admission and (2) continuous deterioration in clinical and laboratory parameters after the delivery. These two additional findings were very helpful in making the clinical diagnosis of PP-TMA.

The diagnostic dilemmas in PP-TMA are heterogeneity in clinical presentations and sharing of common clinical features with preeclampsia, eclampsia and hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome which are more common clinical syndromes in obstetric patients. The prevalence of preeclampsia found to be 3%–5% and usually presents after 20 weeks of gestation. Eclampsia is usually characterized by the occurrence of generalized seizure during pregnancy or postpartum in a woman who has had or subsequently develops preeclampsia. Preeclampsia in 2% of cases may also present with seizures. HELLP syndrome usually a severe preeclampsia with the features of MAHA, liver abnormalities and thrombocytopenia. In HELLP syndrome usually, platelet count remains below 100 × 10^9/L but may go down to 50 × 10^9/L in severe preeclampsia. Preeclampsia mainly presents with mild thrombocytopenia while patients with eclampsia/HELLP syndrome may present with mild to moderate thrombocytopenia. Chandran et al. reported a spontaneous recovery in platelet count 5 days after delivery or 4 days after the platelet count nadir. In HELLP syndrome, nadir platelet count was mainly observed on postpartum day one and platelet count recovered by postpartum day 1. Hemolytic anemia in preeclampsia is less common than thrombocytopenia while it is a defining feature in HELLP syndrome. The severity of hemolysis is usually measured by serum LDH. Usually, in most cases of HELLP syndrome and preeclampsia, there is a prompt spontaneous clinical improvement in a patient within 2–3 days after the delivery while in PP-HUS condition deteriorates after the delivery. Thus, in many cases, the course of illness following delivery has been established as an important determinant for the distinction between HUS and other pregnancy-related syndromes. In published reports, pregnancy has been the underlying cause in 10%–20% of aHUS in adult females and most commonly it presents during the postpartum period. Bell et al. and others have also reported the same.

In 2016, the American Society for Apheresis graded PP-HUS into two categories. Autoimmune antibody associated (anti-factor-H autoantibody) PP-HUS was graded in category I indication for performing PE while complement gene factor mutation associated PP-HUS was graded in category III. Level III diseases...
are those in which existing evidence is insufficient.\textsuperscript{[24]} In a resource-limited country like India, we would like to suggest starting PE soon for a better outcome than to wait for the definitive diagnosis of HUS using complement gene mutation analysis and ADAMTS13 activity estimation.

PE has been found to be effective in our patient population using fresh-frozen plasma as the replacement fluid (fresh-frozen plasma 80\% and normal saline 20\%). Response of PE was adequate in four of seven (58\%) patients in whom platelet count, serum LDH, and serum creatinine values reached within normal range while in remaining three patients (42\%) adequate response was observed in terms of normalization of platelet count and serum LDH values but no positive response was noted in renal parameters. Thus, PE was completely effective in four cases only, while in remaining three cases, it was able to prevent hemolysis but could not give a positive renal response. The three cases were discharged with the final diagnosis of end-stage renal disease (ESRD) and became dialysis dependent. Fakhouri \textit{et al}. also reported that 76\% of postpartum aHUS patients developed ESRD despite receiving PE.\textsuperscript{[7]} Ineffectiveness of PE has been demonstrated in some other published findings also.\textsuperscript{[8,9]}

Seeing the pathophysiology of complement dysregulation and poor response to PE, anecdotal reports suggest effective use of C5 monoclonal antibody (eculizumab) in the treatment of aHUS. Recently published data suggest the superiority of eculizumab over the PE in terms of positive renal response and suggest the pregnancy-associated aHUS is not different from other types of aHUS.\textsuperscript{[25]} Huerta \textit{et al}. and Bruel \textit{et al}. demonstrated poor response of PE in pregnancy-associated aHUS.\textsuperscript{[8,9]}

In our study also, 42\% of the patient did not give response to PE but 58\% of patients gave adequate response. This could be an encouraging result in a country like India where neither the diagnostic tests are accessible to most of the patients nor the definitive immunosuppressive treatment (Eculizumab) is available to most of the patients. Thus, in the current scenario of management of postpartum TMAs in a developing country like India, we still suggest PE a vital life-saving procedure.

By and large, apheresis platforms in India are mainly used for plateletpheresis. Very few centers in India are using it for other therapeutic purposes. That's the main reason why most of the clinicians are unaware of its vital utility in postpartum TMAs. Usually, if PE is done by an expert apheresis specialist, the compliance to PE remains high as we had most of the procedures without any complication except one episode of allergic reaction wherein patient was managed conservatively. In our patient population, we started PE within couple of days of making the clinical diagnosis. Compliance and response to PE in our patient population were good.

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\textbf{Figure 1: Platelet count during plasma exchange}  
\textbf{Figure 2: Serum lactate dehydrogenase during plasma exchange}  
\textbf{Figure 3: Serum creatinine during plasma exchange}  
\textbf{Figure 4: Hemoglobin during plasma exchange}
**Conclusion**

Postpartum TMAs is an uncommon disorder associated with pregnancy but carries high risk of mortality. PE is life-saving in such patients. High degree of suspicion of postpartum TMAs and early start of PE in a case of thrombocytopenia during peripartum period were crucial for a successful outcome in our patient population. The common clinical syndromes during postpartum period which makes it difficult to diagnose Postpartum TMAs from HELLP syndrome and eclampsia. However, these disorders usually recover spontaneously after delivery, while in Postpartum TMAs, there is no spontaneous recovery. For clinical diagnosis and early start of PE, we mainly focused on laboratory and clinical parameters such as (1) thrombocytopenia, (2) MAHA, (3) acute renal abnormalities, and (4) postpartum continuous deterioration of clinical symptoms and signs. We could not do ADAMTS13 and complement factor gene mutation analysis to start PE. Thus, it is not the name of definitive diagnosis, but the quick clinical diagnosis and the early initiation of PE were crucial in the successful management of postpartum TMAs.

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**Conflicts of interest**

There are no conflicts of interest.

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