Hemolytic events during therapeutic plasma exchange: Root cause analysis

Sir,

Hemolytic reactions are often reported in transfusion practices, but it is a rare phenomenon during therapeutic plasma exchange (TPE). Although it is reported using membrane filtration method of TPE, it is infrequent and rarely in apheresis procedure using the continuous centrifugation method. We witnessed two unusual events of hemolysis during TPE in two different patients on the same day in the Department of Transfusion Medicine, in a multi-organ transplant center in South India.

The first patient, a 28-year-old male, was admitted with yellow phosphorus poisoning-induced acute liver failure and was undergoing 3rd cycle of TPE. The procedure was uneventful till 15 min; 400 ml normal saline was being given as initial replacement fluid and then switched to 5% albumin. Waste bag started showing reddish discoloration [Figure 1a] and hemolysis alarm at approximate 150 ml of 5% human albumin solution (Seroalbumin, India) infusion. The procedure was paused and was checked for possible causes of hemolysis due to patient, equipment, procedure, drugs, or replacement fluids. The procedure was aborted at whole blood (WB) processed 1023 ml and plasma removed 631 ml. The patient did not had any change in vitals or signs and symptoms, suggestive of hemolytic reaction. Post-TPE, the patient samples showed pink discoloration. There was no drop of hematocrit or laboratory picture of hemolysis. There was no plasma or any other blood component transfusion. There were no signs and symptoms or laboratory parameters suggestive of acute hemolytic reaction.

Second case, on the same day afternoon, a 58-year-old female presented with early graft rejection postliver transplant who was on regular TPE for past 2 weeks with 5% albumin and fresh-frozen plasma as replacement fluids. Procedure started with replacement fluid as 5% albumin and after 15 min alarm – “Red cell detected in plasma line” came, and hemolyzed plasma was noted in waste bag [Figure 1a] and centrifugation chamber. Procedure was paused as per instruction manual and was investigated for possible causes of hemolysis as shown in Figure 1b; when procedure was resumed with discontinuation of 5% albumin and fresh-frozen plasma units, the red cell detector kept on giving alarms, so procedures had to be discontinued at 0.5 plasma volume exchange. There was a drop of hemoglobin from 8.7 g/dl to 8.3 g/dl and total and direct bilirubin rose from 13.27 g/dl and 10.24 g/dl to 18.82 g/dl and 16.38 g/dl, respectively, which may be attributed to either due to graft dysfunction and/or hemolysis. However, the patient’s vitals remained stable during the full procedure. Reddish discoloration was noted on centrifugation of postprocedure urine and plasma samples which was cleared by next morning. Repeat TPE procedure was performed next day which was completed uneventfully with no signs of hemolysis.

The procedures were being performed using Spectra Optia (Terumo BCT, Lakewood, USA) and both patients were admitted in medical and liver transplant intensive care unit, respectively, and had no previous clinical and laboratory features of hemolysis before starting the procedures.

On further investigation, we found that there was an emergency change in brand of 5% human albumin solution from Baxter AG (Vienna, Austria) to an Indian brand seroalbumin (Virchow Biotech Pvt. Ltd., Andhra Pradesh, India) due to the nonavailability of our routine supplies. Significant correlation was noticed between time of hemolysis and infusion of 5% albumin.

Laboratory investigation for hemolysis workup showed reddish discoloration in plasma color in both patients postprocedure samples. Samples were taken from used
normal saline, anticoagulant, and 5% albumin and were checked for quality and hemolysis test. About 5% albumin on centrifugation with red cells at 2000 rpm for 10 min showed pinkish discoloration. Biochemical analysis of 5% albumin solution showed sodium (Na) concentration – 22.5 mmol/L, potassium (K) – 0, and chloride (Cl) – 6.0 mmol/L which confirmed our suspicion of hemolysis due to hyposmolality of albumin solution. Serum albumin levels were 4.0 g/dl which was less than 80% of total protein content (5.2 g/dl).

Incidence of hemolysis varies widely based on the method of TPE. Yeh et al. noticed higher frequency of 35.4% hemolysis during TPE using double filtration method.[2] Interestingly, hemolytic reaction during TPE has been noted in the United States between 1994 and 1998.[3,4] However, these reports were due to 25% albumin diluted to 5% albumin with sterile water. As per the guidelines for quality control testing of human albumin solution, 96% of the protein content should be albumin and normal sodium levels are 130–160 mmol/L.[5] Biochemical analysis report of the used albumin showed failure of quality control with low sodium and albumin content in the bottle. As an immediate corrective action, the remaining stocks were returned to supplier with analysis report for further action and previous supply of 5% albumin was resumed.

The case highlights the importance of root cause analysis of possible factors contributing to hemolysis or hemolytic reaction[1,2] during TPE [Figure 1b]. Quality control checks should be put on human albumin as well as other commercial solutions used in therapeutic apheresis procedures to ensure patient safety.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/ have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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Drugs / Fluids
- Tonicity of replacement fluids used
- ABO incompatibility blood component X
- Drug intake by patient X

Patient related X
- G6PD deficiency
- Hereditary spherocytosis
- Sickle cell anaemia

Kink in the tubing
- Faulty clamping
- High blood inflow rate
- Peripheral venous access

Equipment and Kit X
- Faulty kit installation

Technical X
- Alarms & Trouble Shoots

Method X
- Centrifugal/ Membrane Filtration
- Continuous/ Intermittent Flow
- Conventional Plasmapheresis / Cascade plasmapheresis / immunoabsorption

Figure 1b: Fishbone diagram used for the analysis of hemolysis during therapeutic plasma exchange
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