Washed RBCs Prevent Recurrent Acute Hypotensive Transfusion Reactions

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ABSTRACT

Objectives: To examine whether a liver transplant patient, who was not taking an angiotensin-converting enzyme inhibitor and developed two episodes of hypotension with systolic pressure in the 50s within minutes of starting an RBC transfusion, may have had a disturbance in the production and metabolism of bradykinin and des-Arg9-BK.

Methods: All patient information was obtained by reviewing the electronic medical record, the transfusion service database, and transfusion reaction investigation records.

Results: The blood pressure returned to normal once the transfusions were discontinued. In an effort to mitigate the acute hypotension, the blood products were washed. Subsequently, the patient received three additional packed RBC transfusions without further incidents of hypotension.

Conclusions: Our experience suggests that washing the products was an acceptable and effective preventative measure to avoid further acute hypotensive transfusion reactions in patients unable to metabolize these vasodilators present in the donor units.

Hypotension may be a manifestation of different types of transfusion reactions such as acute hemolysis, transfusion-related acute lung injury, bacterial contamination of platelets, anaphylaxis, and acute hypotension. In all but the latter type of reaction, other signs and symptoms are usually predominant and often precede the drop in blood pressure. Acute hypotensive transfusion reactions (AHTRs) are characterized by the early and abrupt onset of hypotension, which is often severe, with a drop of the systolic blood pressure below 80 mm Hg. While the hypotension may be isolated and is the predominant symptom, the patient may also experience lightheadedness, dizziness, and anxiety.1 Unlike the other reactions mentioned above, once the transfusion is stopped in an AHTR, the hypotension rapidly resolves without specific therapy.2 Although no particular treatment for AHTR exists, washing packed RBCs (PRBCs) has been suggested to prevent recurrence but without reported evidence of benefit. Implementing a kallikrein blockade may prevent these reactions; however, this approach is experimental.

Bradykinin (BK) has been considered a mediator of an AHTR, especially in those patients taking an angiotensin-converting enzyme (ACE) inhibitor or those who may have impaired alternate pathways of BK metabolism.3 BK is a vasoactive peptide that binds to receptors on the vascular endothelium and causes vasodilation. These native receptors are called B2 receptors, in distinction from cytokine-inducible B1 receptors. BK is produced from the activation of factor XII, which may be activated by interacting with the negatively charged surfaces of tubing, blood storage bags, dialysis membranes, or leukoreduction filters.2 Once activated, factor XIIa transforms prekallikrein into the active form, kallikrein. Kallikrein then converts high-molecular-weight kininogen into BK.
BK activity is normally limited to the site of formation because it is degraded rapidly by three main enzymes: kininase II ACE, aminopeptidase P (APP), and carboxypeptidase N. Each enzyme is responsible for BK degradation to varying degrees; ACE is responsible for 75%, APP for 20%, and carboxypeptidase N for the remainder. Carboxypeptidase N converts BK into its vasoactive metabolite, des-Arg^9^B-K, which is subsequently inactivated by both ACE and APP. Thus, if an ACE inhibitor is present or there are dysfunctional polymorphisms of APP or ACE that render the enzymes less efficient at metabolizing des-Arg^9^B-K, a larger amount of des-Arg^9^B-K will be present. This increase may result in the development of hypotension, especially in those patients with comorbidities that upregulate the inducible B1 receptors.\(^3,5\)

**Case Report**

A 66-year-old woman was admitted for altered mental status due to hepatic encephalopathy. The patient had a medical history significant for end-stage liver disease secondary to hepatitis C and alcohol abuse. The patient had previously received an orthotopic liver transplant with subsequent recurrent cirrhosis. She also had hemodialysis-dependent end-stage renal disease, gastrointestinal hemorrhage secondary to varices, previous spontaneous bacterial peritonitis, portal vein thrombosis, and anemia. The patient had positive blood cultures for Gram-positive cocci and was intubated for respiratory failure. Due to a hemoglobin of 5.1 g/dL, a unit of PRBCs was ordered to be transfused.

Almost immediately from the start of transfusion of the first unit, the critical care team noted an abrupt drop in her blood pressure. Prior to transfusion, her blood pressure was 93/43 mm Hg; one minute after the transfusion was started, her blood pressure dropped to 55/29 mm Hg. The transfusion was stopped immediately, and her blood pressure returned to 81/49 mm Hg within 30 minutes. No other symptoms were reported, and only minimal changes in her temperature and pulse were noted. Since the patient’s hemoglobin remained low, transfusion of a second unit of PRBCs was started 5 hours after the first transfusion reaction. No premedication was given prior to the first transfusion, but the patient did receive 50 mg diphenhydramine before the second transfusion. Similarly to the first transfusion, the patient’s blood pressure began to drop 2 minutes after starting the transfusion, from 116/47 mm Hg to 72/33 mm Hg, and it was stopped immediately. Forty-five minutes after the transfusion was stopped, her blood pressure returned to 117/48 mm Hg. At that time, the clinicians believed the hypotension was evidence of vasomotor instability related to her underlying conditions and attended to her fluid status and antibiotic medications. A third attempt at transfusion was made 14 hours after the second reaction. The patient was premedicated with 50 mg diphenhydramine and 100 mg acetaminophen. Again, hypotension was observed, her blood pressure decreased from 120/53 mm Hg to 80/32 mm Hg 5 minutes after the transfusion began, and her blood pressure returned to 120/70 mm Hg 20 minutes after the transfusion was stopped. Blood pressure support with pressors was not implemented for any of these reactions. All transfused units were prestorage leukoreduced.

The clinical team reported the third event as a transfusion reaction. Hemolytic reactions were ruled out, and the transfusion medicine consultation recommended a trial of washed PRBCs for recurrent AHTRs. Our RBC procedure for PRBC washing employs 1 L of 0.9% NaCl using the COBE 2991 Model I Cell Processor (Terumo BCT, Lakewood, CO). Initially, one unit was washed and transfused 3.5 hours after the third AHTR without incident. Two additional units of PRBCs were then washed, both of which were transfused later that same day, also without causing further AHTRs. The three washed PRBCs were transfused without premedication. Her hemoglobin rose to 9.7 g/dL. The team decided to continue using washed blood and considered using unwashed blood if the patient’s systemic inflammatory response syndrome (SIRS) improved. However, 4 days after her first AHTR, her SIRS worsened, resulting in further deterioration of her respiration and liver function; the patient’s family decided to provide comfort care only, and she died after extubation.

**Discussion**

The occurrence of AHTR has been well documented, especially in patients undergoing apheresis or dialysis, those taking ACE inhibitors,\(^6,7\) and even patients not receiving ACE inhibitors.\(^8\) The mechanism of AHTRs is likely caused by multiple factors. The most likely causes involve variables such as the degree of activation of factor XII in donor plasma, the charge of filters used in leukoreduction, the type of tubing or surfaces to which the blood products have come in contact, and especially inherited or acquired defects in the enzymes used for the metabolism of BK in the recipients, predominantly caused by ACE inhibitor drugs.\(^2\) Increasing attention has been focused on abnormalities affecting the degradation of the biologically active metabolite des-Arg^9^B-K, which is able to bind to the inducible B1 receptors of the endothelium.\(^5,9,10\) Due to the accumulation of BK metabolites generated by the collection process or during storage, patients with such abnormalities are less able to clear des-Arg^9^B-K. Higher plasma levels of des-Arg^9^B-K cause increased activation of B1 receptors that results in vasodilation, making acute hypotension more likely.
Doria et al.\(^3\) reported a patient with end-stage liver disease who experienced an AHTR during liver transplant surgery. Although the patient was taking an ACE inhibitor, ACE and APP activity in serum 14 and 19 days after the drug was discontinued were in the 1st and 15th percentiles, respectively. These results provide evidence that patients with end-stage liver disease may have decreased production of ACE and APP, making them more prone to acute hypotension. Although our patient was not taking an ACE inhibitor and her APP and ACE activity levels were not measured, she also had worsening liver disease as the presumed cause of a susceptibility to these reactions along with her underlying acute illness.

Our patient had received numerous PRBC transfusions prior to her development of SIRS. These multiple transfusions may have led to an upregulation of B1 receptors from transfusion-associated cytokines. This increase in B1 receptors may have increased her susceptibility to an AHTR by more readily reacting with the vasoactive metabolite, des-Arg\(^9\)-BK. The patient’s diagnosis of AHTR was made based on the isolated symptom of severe hypotension, which had rapid resolution after cessation of the transfusions. The success of washing the units before transfusion suggests that the patient’s recurrent AHTR was due to an increased susceptibility to elevated levels of BK or its metabolites caused by offending agents in the unit’s supernatant. The effect of leukoreduction on the incidence of AHTR is unclear since AHTRs still occur at our institution despite universal use of prestorage leukoreduced blood products. Since these reactions are infrequent, we were unable to quantify the current incidence compared with the incidence before prestorage leukoreduction.

Our case illustrates that acquired recurrent AHTRs may be unrelated to the use of ACE inhibitors and perhaps is linked to worsening liver synthetic function or the cytokine storm in SIRS. Our experience shows that washing PRBCs for patients with recurrent hypotensive transfusion reactions may be an effective method to prevent further reactions.

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References