MEDICAL CONSIDERATIONS

Background

Massive transfusion, in support of massive hemorrhage protocols (MHPs), is generally defined as the transfusion of greater than 8 Red Blood Cell (RBC) units in an adult recipient in <24 hours or the acute transfusion of >4 RBC units within 1 hour. Because the clinical impact of massive transfusion also depends on the bleeding rate, some clinicians define massive transfusion as a loss of 50% of blood volume in 3 hours or a bleeding rate of greater than 150 mL/minute.

The physical characteristics of stored blood attributable to anticoagulant-preservative solutions, storage-related metabolic processes, and temperature requirements for storage can also alter recipient physiology when stored blood is infused in a large volume. This is particularly evident when transfusions are administered using newer devices capable of rapid infusion rates of up to 300 mL/minute. The critical status of patients requiring massive transfusion makes them especially susceptible to these potential adverse effects of blood transfusion.

Citrate Toxicity

Citrate toxicity manifested by hypocalcemia and hypomagnesemia is an important physiologic consideration for the patient undergoing massive transfusion. Citrate toxicity manifests when large volumes of citrated blood and blood components are transfused rapidly, causing a rise in plasma citrate levels and binding calcium, resulting in hypocalcemia. The chelation effect of citrate, which reduces calcium and magnesium availability, can decrease myocardial contractility, and predispose the patient to arrhythmias.1,2
In addition, hypocalcemic patients experience symptoms of perioral and peripheral tingling, shivering, and lightheadedness, followed by muscle cramps and nausea. Consideration is also needed for patients with liver impairment, especially during the anhepatic phase of liver transplantation, because these patients have markedly impaired citrate clearance and, therefore, greater susceptibility to these adverse effects.

Despite the critical role of calcium in coagulation pathways, the degree of hypocalcemia associated with massive transfusion will not impair function of the coagulation system. The recipient would suffer fatal consequences of hypocalcemia due to depressed cardiovascular function before the development of coagulation derangement.

Citrate is metabolized through the Krebs cycle by cells rich in mitochondria (liver, kidney, and muscle). Adequate perfusion of hepatic vascular beds with hepatocyte citrate uptake is the most important mechanism for avoiding citrate toxicity. Infusion of blood at rates up to 30 mL/kg/hour is generally well tolerated by physiologically intact patients with adequate hepatic perfusion and hepatocellular function. When that rate is exceeded, hemodynamic instability may occur as blood citrate loading exceeds citrate clearance, yielding elevated blood citrate levels and resulting hypocalcemia.

Patients receiving such high rates of blood transfusion should be monitored by measurement of ionized calcium or analysis of the QT interval on the electrocardiogram. Poor outcomes are associated with ionized calcium levels less than 0.5 mmol/L; however, the critical value in humans is not clear. Intravenous calcium therapy with calcium gluconate or calcium chloride under careful management should be considered. Usually, treatment is instituted at a substantially higher level of 0.8 to 0.9 mmol/L. In the presence of ongoing bleeding and anticipated further transfusion, calcium supplementation may be given at even higher levels. In addition, slowing the transfusion during massive transfusion should be considered.

There are no readily available methods for monitoring the magnesium level. Magnesium supplementation should be considered.
when the QT interval, blood pressure, or other cardiac monitors suggest hypomagnesemia.

**Potassium Flux**

Impaired function of the membrane Na⁺-K⁺ ion pump at low temperatures causes movement of K⁺ to the extracellular fluid compartment during blood storage. Although net potassium load associated with transfusion is unchanged, the supernatant plasma and preservative fluid of a unit of blood stored for 4 to 5 weeks can contain 5 to 7 mmol of potassium.

Potassium is cleared by renal mechanisms; however, renal excretion is too slow to be clinically important in patients with acute hyperkalemia associated with massive transfusion. Renal elimination of potassium is also likely to be diminished if the patient is hypotensive. The most important clearance effect is the cellular redistribution of potassium, especially reuptake by transfused red cells from units of irradiated and stored blood, but this mechanism is too slow to have an impact in the acute situation.

In adults, infusion of stored RBC units usually has minimal impact on the serum potassium level. Transfusion-related hyperkalemia can be clinically important, possibly resulting in cardiac arrhythmia, in neonates or very small or young children undergoing rapid transfusion. Rare case reports have also documented transfusion-related hyperkalemia associated with rapid infusion of stored blood in adults. Currently, there is no recommendation for prophylactic treatment or further processing of blood for massively transfused adult patients on the basis of this consideration. However, transfusing neonates at a rate of 0.5 mL/kg/minute is considered safe until the expiration date of the product.

The urgency of massive transfusion in most patients prohibits preparation of an ideal unit; hence, the transfusionist must be alert to the potential for hyperkalemia and appropriate management of this problem.