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RBC Transfusions for Neonates: Are RBCs Stored in Additive Solutions Safe?

Background

Historically, hospitals often transfused preterm infants and very low birth weight (VLBW) neonates (infants weighing <1500 g) with red blood cells (RBCs) stored in CPD or CPDA-1. This practice was based on the perceived harmful effect of the additive solutions [e.g. Adsol (AS-1), Nutricel (AS-3), Optisol (AS-5)] that are now routinely used for RBCs to allow a maximum shelf life of 42 days.

Neonates, particularly those who are premature, have immature immune and metabolic processes and are still undergoing rapid neurodevelopment. The additive solutions (AS) contain mannitol and/or adenine (see Table 1). The perception is that these solutes may not be metabolized by the neonate receiving multiple transfusions and could result in changes to intracerebral pressure or place the infant at risk for liver or kidney damage. Possible hyperkalemia from the storage duration of the AS units is another concern.

For premature infants, particularly VLBW neonates, anemia is common due to such factors as lower hemoglobin at birth, blood losses from frequent phlebotomy and management of illnesses, and a decreased capacity to increase plasma erythropoietin. Consequently, most RBC transfusions to neonates are 'top-up' transfusions (repeated small volumes of RBCs, up to 20 mL/kg). For these small volume transfusions, is there evidence to support the use of RBCs stored in additive solution?

Table 1. Comparison of CPD, CPDA-1, AS-1, AS-3, and AS-5 anticoagulant preservative solutions*

	CPD^f	CPDA-1	AS-1 (Adsol)^f	AS-3 (Nutricel)^f	AS-5 Optisol
Volume (mL)	70	70	111	111	111
Dextrose	1780 mg	2233 mg	2444 mg	1222 mg	1000 mg
Adenine	0 mg	19.2 mg	30 mg	33.3 mg	33.3 mg
Mannitol	0 mg	0 mg	833 mg	0 mg	583 mg
Monobasic Sodium Phosphate	155 mg	156 mg	0 mg	307 mg	0 mg
Sodium Chloride	0 mg	0 mg	1000 mg	456 mg	974 mg
Trisodium Citrate	1840 mg	1844 mg	0 mg	653 mg	0 mg
Citric Acid	209 mg	229 mg	0 mg	46.7 mg	0 mg
Shelf Life	21 days	35 days	42 days	42 days	42 days

*Table adopted from Pediatric Transfusion: A Handbook, 5th edition p. 12. (Ref 1)
^{f}Versiti manufacturers CPD, AS-1 and AS-3 RBCs.

Evidence Supporting the Safety of RBCs in Additive Solution for Neonates

Since the introduction of AS, many years of experience as well as several studies have confirmed that small volume transfusions (<20 mL/kg) of unmodified RBCs stored in AS are safe and well tolerated by the neonate.[2-5] Estimates from theoretical calculations have demonstrated that the quantity of additives infused during a transfusion of 15 mL/kg of either AS-1 or AS-3 RBC to a 1 kg neonate are far below that of toxic levels.[1-3] (See Table 2)

Several subsequent in vivo studies have supported these calculations. Changes in pH, glucose, lactate, calcium, sodium, and potassium were minimal post transfusion of AS RBCs.[3] In addition, use of RBCs stored in AS has resulted in reduced donor exposure for the infant. In one study, mean donor exposure was 1.6 for infants given AS-1 RBC transfusions compared to mean of 3.7 donors when CPDA-1 RBCs were transfused.[4]

TABLE 2. Quantity (total mg/kg) of additives infused during a transfusion of 15 mL per kg of AS-1 or AS-3 RBCs at Hct of 60%*

Additive	AS-1	AS-3	Toxic dose (mg/kg)
NaCl	54.0	24.6	137 /day
Dextrose	132.0	66.0	240 /hr
Adenine	1.6	1.8	15 /dose
Citrate	Trace	37.8	180 /hr
Phosphate	Trace	16.6	>60 /day
Mannitol	45.0	None	360 /day

*Accuracy of toxic dose is difficult to predict for transfusions to individual infants because infusion rates generally are slow, permitting the metabolism and distribution of additives from blood into extravascular sites. Moreover, dextrose, adenine, and phosphate enter RBCs and are somewhat sequestered and not immediately available in the extracellular solution.[1]

Another apprehension with the use of older AS RBC units, especially those near expiration, is the load of potassium that the infant may receive during the transfusion. Surprisingly, a 10 mL/kg aliquot prepared from a 42-day old AS RBC unit is estimated to deliver 0.1 mmol/L of potassium. This amount is less than the daily potassium requirement of 2-3 mmol/L for a 1 kg neonate.[6]

Over time, most hospitals have become receptive to using RBCs stored in AS for neonates. A 2008 survey of 47 University Health System hospitals showed that most centers (28 or 60%) were already using or willing to accept unmodified RBCs stored in AS-1, AS-3, or AS-5 for small volume neonatal transfusions.[7] A subsequent survey in 2017 of 35 AABB-accredited pediatric hospitals in the US found similar findings with 57% of the institutions routinely using RBCs in additive solution for low volume transfusions.[8] Despite the evidence supporting the safe use of AS RBCs for small volume transfusions, universal adoption of this practice though appears to be lagging.

For large volume transfusions (≥20mL/kg) as with exchange transfusion or blood prime for cardiac bypass/extracorporeal membrane oxygenation, the evidence is less clear as to the actual risks. Over the years, a majority of academic pediatric centers have transitioned to use of AS-1 or AS-3 RBCs for large volume transfusion, but provide fresh (e.g., <7-10 days old) AS RBCs in these settings.[8,9] However, based on theoretical concerns cited above, some centers may continue with removal of the additive solutions by either centrifugation or washing before use of the unit for large volume transfusions.

Recently, a single Midwest academic pediatric center retrospectively studied the safety of large volume (≥20 mL/kg) compared to small volume (<20 mL/kg) AS-1 RBC transfusions in patients less than 6 months of age undergoing cardiovascular surgery. A total of 201 transfusion events (large and small volume) in 129 patients were analyzed. Large volume AS-1 RBC transfusions had statistically significant greater change in post-transfusion Na+, K+, glucose, creatinine, arterial HCO3, hemoglobin, and arterial O2 saturation. However, these changes were not considered clinically significant when compared to small volume transfusions, and except for glucose, the values in both groups were within normal limits. In addition, there was no evidence of metabolic complications, nephrotoxicity or increase in intracerebral pressure after the large volume AS-1 RBC transfusions.[10]

This recent retrospective data and a growing number of anecdotal reports of no adverse effects suggests that AS RBCs are safe for even large volume transfusion in neonates. This is an important consideration for some centers who may find it increasingly difficult to obtain RBC units without additive solution and wish to simplify their neonatal transfusion protocols and eliminate the need for dual RBC inventory.

Recommendations:

RBC units stored in AS (e.g. AS-1 or AS-3) are an acceptable choice for small volume transfusion (<20 mL/Kg) to preterm neonates and can safely be used for multiple small volume transfusions to a single neonate.

For large volume transfusions, such as for heart transplant, cardiac surgery, or exchange transfusion, the safety of AS RBC units without removal of the AS (by centrifugation or washing) is less clear. Experience and limited retrospective data suggests that unmodified RBCs stored in AS could also be considered for large volume neonatal transfusions. Transfusion services, in collaboration with their neonatologists, should establish guidelines for neonatal transfusions to optimize care and promote effective inventory management.

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