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Small Volume Transfusions in Neonates: Red Cells in Additive Solution are an Acceptable Choice

by Leon Su, M.D.

Background:

Blood components today are stored in anticoagulant solutions such as ACD, CPD, CP2D, CPDA-1, or additive solutions such as AS-1, AS-3, AS-5. The formulation of some of these anticoagulant solutions can be seen in TABLE 1.

TABLE 1. Formulation of anticoagulant-preservative solutions in blood collection sets (Ref 1)

Constituent	CPDA*	AS-1†	AS-3†	AS-5†
Volume (mL)	63	100	100	100
Sodium Chloride (mg)	None	900	410	877
Dextrose (mg)	2000	2200	1100	900
Adenine (mg)	17.3	27	30	30
Mannitol (mg)	None	750	None	525
Trisodium citrate (mg)	1660	None	588	None
Citric acid (mg)	206	None	42	None
Sodium phosphate (monobasic) (mg)	140	None	276	None

** Approximately 450 mL of donor blood is drawn into 63 mL of CPDA. A unit of RBCs (Hct ≅ 70%) is prepared by centrifugation and removal of most plasma.*

† When AS-1 or AS-5 is used, 450 mL of donor blood is first drawn into 63 mL of CPD, which is identical to CPDA except it contains 1610 mg of dextrose per 63 mL and has no adenine. When AS-3 is used, donor blood is drawn into CP2D, which is identical to CPD except it contains double the amount of dextrose. After centrifugation and removal of nearly all plasma, RBCs are resuspended in 100 mL of the additive solution (AS-1, AS-3, or AS-5) at a Hct ≅ 55 to 60 percent.

Traditionally, neonates (defined as younger than 4 months old) were preferentially transfused with CPD, CP2D, or CPDA-1 blood components. The rationale was based on the concern that additive solutions contained additional solutes, such as mannitol and adenine, that were believed to result in potentially harmful changes to intracerebral pressure or lead to an increased risk for hepatic or renal toxicities in neonates. However, in recent years, there has been an accumulation of literature suggesting that blood components stored in additive solutions are safe and efficacious for small volume transfusions in neonates. This document summarizes and puts forth several recommendations by the medical affairs division of United Blood Services/Blood Systems, supported by the recent evidence on anticoagulant-preservatives and additive solutions in blood components as it relates to neonatal transfusion.

About the Author

Dr. Leon Su is the medical director for the United Blood Services center in Arizona. Board-certified in transfusion medicine, he is also a part-time medical staff member at both Phoenix Children's Hospital and Mayo Clinic Hospital. He holds academic appointments with the Mayo Clinic College of Medicine, the University of Arizona College of Medicine and the University of New Mexico School of Medicine.

Recommendations:

These recommendations were developed using the classifications and levels of evidence defined in the chart at the end of this document.

1. **Recommendation:** *RBC units collected in additive solutions such as AS-1 or AS-3 can be used for multiple, small volume transfusions in all neonates including preterm infants.*
   Classification of Recommendation: *IIa*
   Level of Evidence: *A*

Several studies have demonstrated the safety of AS-1 and AS-3 units for small-volume, RBC transfusions. It has been proposed that the dose of additive media infused during a typical small-volume RBC transfusion is estimated to be far below the levels thought to be toxic (TABLE 2). Coupled with a typical rate of infusion at 2-4 hours for most small-volume transfusions, many transfusion experts believe that the quantity of additives received by the transfused pediatric patient would be negligible. The same opinion is also applied to pre-term infants where there has been no evidence to suggest that pre-term infants are unable to properly metabolize or excrete additives, even when undergoing multiple small-volume transfusions. These opinions have been proven correct by several randomized control studies documenting the safety of AS-1 and AS-3 RBC units in neonates receiving small volume transfusions (Ref 1-7). Results from these studies demonstrate that neonates receiving AS units compared to CPDA-1 units have similar levels of post-transfusion HCT, pH, plasma Na, K, Ca, lactate and glucose levels.

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% (Ref 1)

Additive	AS-1	AS-3	Toxic dose*
NaCl	42	7.5	137 mg/kg/day
Dextrose	129	23	240 mg/kg/hr
Adenine	0.6	0.6	15 mg/kg/dose
Citrate	9.8	12.6	180 mg/kg/hr
Phosphate	2.0	5.6	>60 mg/kg/day
Mannitol	33	0	360 mg/kg/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. Potential toxic doses taken from Luban NLC et al. Transfusion 1991;31:229-35.*

With today's safety measures on the donor blood supply, there is minimal concern regarding the safety of units from multiple donors. Nevertheless, while the risk of complications is very low, it stands to reason that, when possible, it is ideal to attempt to minimize the number of donor exposures. In the same studies above, use of AS units up to 42 days decreased the number of donor exposures compared to the exclusive use of CPDA-1 units stored less than 7 days. From published studies to date, the safety profile and outcomes of neonates receiving AS units stored up to 42 days compared favorably to neonates receiving only fresh CPDA-1 units (Ref 5-7).

2. **Recommendation:** *RBC units collected in additive solutions such as AS-1 or AS-3 can be used for large volume transfusions, such as in ECMO/CPB or exchange transfusion, in all neonates including preterm infants.*
   Classification of Recommendation: *IIb*
   Level of Evidence: *B*

The evidence supporting the use of AS units in large volume transfusions such as in ECMO/CPB or exchange transfusion is not well established. However, one abstract from the Children's Hospital of Philadelphia reports data showing that AS-1 and AS-3 units were tolerated as well as CPDA-1 units in infants on ECMO (Ref 8). Their study showed that the post-transfusion laboratory values were comparable in both groups.

Summary of Recommendations:

For small volume transfusions in neonates including preterm infants, red cells collected and stored in additive solution are an acceptable blood product choice. Neonates requiring multiple, small volume transfusions can have aliquots made from the same parent bag stored in AS and used up until the day of expiration to minimize donor exposures. AS-3 may be preferentially chosen over AS-1 for neonatal transfusions because of the theoretical concern over mannitol content which is absent in AS-3 but present in AS-1. However, the existing literature suggests safety of both additive solutions in the context of multiple, small volume transfusions.

For large volume transfusions such as in ECMO/CPB procedures or exchange transfusion, AS units could be considered for use in all neonates including preterm infants based on anecdotal evidence and small observational studies. The evidence supporting the use of AS units in large volume transfusions are not as well established as they are in the setting of multiple, small volume transfusions.

Classification of Recommendations:

Class I:	Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective.
Class II:	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment. **IIa.** Weight of evidence/opinion is in favor of usefulness/efficacy. **IIb.** Usefulness/efficacy is less well established by evidence/opinion.
Class III:	Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and, in some cases, may be harmful.

Level of Evidence:

Level of Evidence A	Data derived from multiple randomized clinical trials
Level of Evidence B	Data derived from a single randomized trial, or non-randomized studies
Level of Evidence C	Consensus opinion of experts

References

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8. *Eder A, et al. Comparison of CPDA vs. AS red cell transfusion to infants on ECMO. http://www.cbbsweb.org/enews/cpda_asrbcs.pdf*
9. *Josephson CD, Strauss RG. Transfusion of Neonates and Pediatric Patients. In Hillyer C, et al (eds):Blood Banking and Transfusion Medicine, 2nd edition. Phila-delphia, PA. Elsevier 2007;513-4.*