THE USE OF RED CELL ADDITIVE SOLUTIONS AND SPECIAL ATTRIBUTES IN NEONATAL PATIENTS

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Introduction

- **Currently many blood banks manage two RBC inventories. In an attempt to provide low additive solution (AS) containing RBC units to neonatal patients.**

- **Although older publications suggest a safety benefit to decreasing AS exposure, there are no published studies showing overt clinical complications with AS exposure in neonatal patients.**

Objectives

- **Discuss/describe different formulations of popular red cell additive solutions and anticoagulant preservative solutions commonly used in neonatal transfusions.**
  - **AS-1**
  - **AS-3**
  - **AS-5**

  Additive Solutions
  - **CPD**
  - **CPDA-1**

  Anticoagulant Preservatives

Objectives

- **Discuss/review literature concerning use of red cell additive solutions for both small and large volume neonatal transfusion.**

- **Discussion will focus on some of the most common concerns associated with transfusion of additive solutions to neonatal patients.**

Objectives

- **Discuss survey results concerning:**
  - **RBC additive of choice for neonatal patients in a variety of clinical settings.**
  - **Policies concerning CMV seronegative blood product usage for neonatal patients.**
  - **Policies concerning irradiated blood product usage for neonatal patients.**

What are RBC Additive Solutions & Anticoagulant Preservatives?

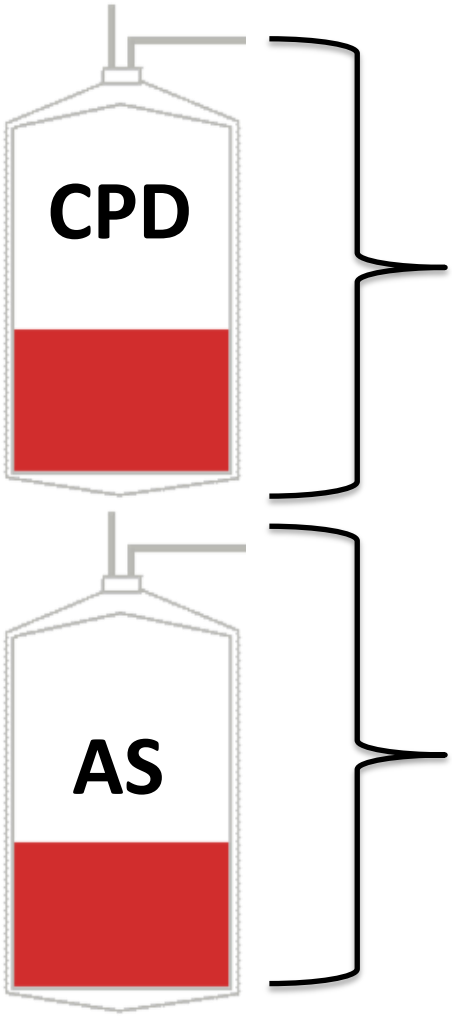
- AS-1: Adsol
- AS-3: Nutricel
- AS-5: Optisol

} Additive Solutions

- CPD
- CPDA-1

} Anticoagulant Preservative

WHAT'S IN THE BAG?



- 225-350 mL RBCs
- Residual Plasma
- No additive solution
- Hct: 65%-80%

- 300-400 mL RBCs
- Residual Plasma
- 100-110 mL of additive solution
- Hct: 55%-65%

Circular of Information for the use of Human Blood and Blood components pg 8-9

CPD Preservatives

ADVANTAGES	DISADVANTAGES
Higher hematocrit (65%~80%).	Shorter expiration date than additive solution RBC units; 21~35 days compared to 42 days.
Safety of CPD is well known.	Increased donor exposure due to shorter shelf life.
No additive solutions.	

Additive Solutions

ADVANTAGES	DISADVANTAGES
Longer expiration date than CPD units; 42 days compared to 21~35 days	Large volume neonatal transfusion (>20-25mL/kg) of AS RBCs has not been studied.
Decreased donor exposure; one unit can be split several times to service one high need pt or several moderate need pt's	Possible exposure to large doses of adenine, dextrose, and mannitol
Several studies exist supporting small volume (<10mL-15mL/kg) AS RBC transfusions are safe for neonatal pt's	Lower hematocrit than CPD RBC units (55%~65%)

Clinical Concerns Associated With AS

1. **Adenine: Metabolites can cause crystals to form in renal tubules causing liver and kidney problems**
2. **Mannitol: large molecule; high osmolality**
   - **Pulls water into vessels**
   - **Concern about causing osmotic diuresis and compromising cerebral blood flow in neonates**

Philps, FS et al. J Pharm Exp Ther, 1952

Clinical Concerns Associated With AS

3. **Potassium: Cardiac arrhythmia**
4. **Hypernatremia: Sodium in the blood product**
5. **Hypocalcemia: Citrate & phosphate chelate patient's calcium**

Philps, FS et al. J Pharm Exp Ther, 1952

Key Differences

	AS-1* (Adsol)	AS-3* (Nutricel)	AS-5* (Optisol)	CPD**	CPDA-1**
Dextrose	2200 mg/100mL	1100 mg/100mL	900 mg/100mL	1610 mg/63mL	2010 mg/63mL
Adenine	27 mg/100mL	30 mg/100mL	30 mg/100mL	0 mg/63mL	17.3 mg/63mL
Mannitol	750 mg/100mL	0 mg/100mL	525 mg/100mL	0 mg/63mL	0 mg/63mL
Monobasic Sodium Phosphate	0 mg/100mL	276 mg/100mL	0 mg/100mL	140 mg/63mL	140 mg/63mL
Sodium Chloride	900 mg/100mL	410 mg/100mL	877 mg/100mL	0 mg/63mL	0 mg/63mL
Sodium Citrate	0 mg/100mL	588 mg/100mL	0 mg/100mL	1660 mg/63mL	1660 mg/63mL
Citric Acid	0 mg/100mL	42mg/100mL	0 mg/100mL	206mg/63mL	206mg/63mL
Shelf Life	42 DAYS	42 DAYS	42 DAYS	21 DAYS	35 DAYS

AABB Technical Manual 17th Edition pg 191 -192

Safety of Red Cells Preserved in Extended Storage Media for Neonatal Transfusions

Luban, Strauss, and Hume

- **Theoretical calculations based on the amounts of additives transfused to neonatal patients in defined clinical settings based on known toxicology of additive solutions.**
  - **First clinical setting: Small volume transfusion (<10mL/kg) given to infant weighing 1 kg, to replace phlebotomy losses.**
  - **Second clinical setting: Exchange transfusion of an infant weighing 3kg, receiving 1 unit of reconstituted whole blood.**
  - **Third clinical setting: Multiple units over prolonged periods of time ex: cardiac bypass or ECMO.**

Luban et al. Transfusion, 1991

Toxic Threshold Calculations: Large Volume Transfusions

Dose of additive (mg/kg)	1 kg infant 10mL/kg AS RBC	3 kg infant Exchange Tx 240mL R-WB, 80%	3 kg infant 2 AS RBC ECMO / CPB Retain 240 mL		Dose judged to pose risk (mg/kg/hr)
Dextrose	86	358	1982	668	**240**
Sodium	28	64	641	224	**137**
Citrate	6.5	173	148	52	**180**
Phosphate	1.3	10	31	10	**>60**
Adenine	0.7	2.6	18	5.6	**15**
Mannitol	22	14	500	176	**360**

Luban et al. Transfusion, 1991

Safety of Red Cells Preserved in Extended Storage Media for Neonatal Transfusions

Luban, Strauss, and Hume

Challenges to accurately estimate additive exposure and asses toxic dose:

- **Clinical setting**
- **Duration of exposure to additive solutions**
- **Physiology**
  - **Bioavailability of solutes**
  - **Intracellular trapping of solutes**
  - **Dispersion to extracellular compartments of solutes**
  - **The protein binding, metabolism, and excretion after transfusion.**
  - **Patient's renal and hepatic status**

Luban et al. Transfusion, 1991

Clinical Studies Support Low Volume Transfusions with Additive RBC Units

Table 3. Small-volume red blood cell transfusions given as stored red blood cells to limit donor exposure without causing apparent adverse effects

Reference	Solution	Storage	Dose	Hct* (%)	Transfusions	Donors
Liu [4]	CPDA-1	≤35 d	15 mL/kg	75	5.6	2.1
Lee [5]	CPDA-1	≤35 d	13 mL/kg	68–75	6.0	2.0
Wood [6]	NR	≤35 d	15 mL/kg	NR	5.6	4.9
Strauss [2]	AS-1	≤42 d	15 mL/kg	85	3.5	1.2
Strauss [3]	AS-3	≤42 d	15 mL/kg	85	3.6	1.3
van Straaten [14]	SAGM	≤35 d	15 mL/kg	NR	3.2	1.1 high risk
	SAGM	≤35 d	15 mL/kg	NR	0.4	1.1 low risk
Mangel [13]	AS-3	≤21 d	7 mL/kg	55–60	4.7	1.7

AS, adenine saline; CPDA, citrate phosphate dextrose adenine; NR, not recorded; SAGM, saline adenine glucose mannitol.

- **Six studies**
  - **Different age of product, type of solution, dose transfused**
  - **No evidence of hyperglycemia, hypoglycemia, hypocalcemia, hyperkalemia, hyponatremia**
  - **No clinical adverse consequences or significant differences in blood chemistry were observed**

Luban et al. Curr Op Hematol, 2002

Blood Component Preferences of Transfusion Services Supporting Infant Transfusions: A University Health System Consortium Benchmarking Study

- **Purpose: The extent of acceptability of RBCs stored in additive solutions for low volume neonatal transfusion among hospitals is currently unknown.**
- **Included questions concerning the use of AS for low volume neonatal transfusion (<20ml/kg).**
- **Survey Results:**
  - **60% accepted the use of at least one (AS-1, AS-3, or AS-5) for neonatal transfusions with a preference for AS-3.**
  - **45% accepted the use of all three additive solutions.**

Fung et el Transfusion, 2010

Blood Component Preferences of Transfusion Services Supporting Infant Transfusions: A University Health System Consortium Benchmarking Study

- **Conclusion: Although many institutions will use AS, many will not**
- **This survey was not designed to determine the reasons for these preferences.**
- **Possible reasons for these preferences may include.**
  - **Lack of awareness of current data concerning the use of AS for neonatal transfusion.**
  - **Lack of acceptance of current data.**
  - **More data may be needed.**

Fung et el Transfusion, 2010

Comparison of CPDA vs. AS Red Cell Transfusion To Infants on ECMO

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Introduction

Transfusion protocols for infants on extracorporeal membrane oxygenation (ECMO) were developed in the absence of definitive evidence to guide decisions. Consequently, practices vary among pediatric institutions with respect to the selection of red cell components (*i.e.*, maximum storage time prior to transfusion; preservative/anticoagulant solution) and further modification of the units (*i.e.*, supernatant removal; washing). Two different transfusion protocols evolved at The Children's Hospital of Philadelphia in an effort to balance disparate concerns among groups of specialist physicians. Reflecting primarily theoretical considerations regarding additive solutions (AS), in particular, their mannitol and adenine content, a protocol for infants in the neonatal intensive care unit specifies type O red cells less than 10 days old collected in CPD or CPDA-1 (CPD/A). If only AS units are available the supernatant is removed prior to transfusion. In contrast, cardiologists and anesthesiologists at our institution preferentially requested AS units over CPD/A units, primarily because of the lower concentration of extracellular potassium and decreased risk of attendant cardiac toxicity following massive transfusion. Consequently, infants in the cardiac intensive care unit (CICU) receive primarily ABO/Rh type-specific red cells, collected in AS-1 or AS-3 (AS1/3); some may also receive CPD/A units based on available inventory. Our CICU experience suggests that infants on ECMO tolerate AS1/3 units as well as CPD/A units. To substantiate the comparative safety of transfusing large volumes of AS1/3 units compared to fresh CPD/A units to infants less than four months on ECMO, a retrospective audit of transfusions in the CICU was conducted.

Methods

Infants in the CICU who received whole unit red cell transfusion on ECMO were selected for retrospective audit. Hemoglobin, sodium, potassium, calcium, glucose and creatinine values were compared before and after the transfusion of CPD/A red cell units or AS1/3 red cell units. Post-transfusion laboratory values were measured within 4 hours of the transfusion. The pre- and post-transfusion mean laboratory values were compared with paired t-tests (one-tailed for hematocrit; two tailed for all other analytes). Pretransfusion laboratory values were subtracted from posttransfusion results to express mean changes in blood chemistry levels, so that a positive value indicates an increase; a negative value, a decrease after transfusion. The mean changes (D) were then compared with unpaired t-tests.

Table 1. Red Cell Transfusions Audited

CPD or CPDA Transfusions				AS-1 or AS-3 Transfusions			
Tx	Patient	Age	Indication for ECMO	Tx	Patient	Age	Indication for ECMO
1	A	2 m	Tetralogy of Fallot/ARDs	1	A	2 m	Tetralogy of Fallot/ARDs
2	B	2 d	Bridge to heart transplant	2	B	2d	Bridge to heart transplant
3	C	3 d	Transposition of the great	3	B		
4	C		arteries	4	E	3m	Bridge to lung transplant
5	D	2d	Cardiac arrest, congenital	5	E		
6	D		heart disease	6	F	5d	Transposition of the great arteries, double outlet right ventricle sp surgery

Table 2. Laboratory Values with Transfusion

	CPD/A			AS1/3		
	Pre	Post	p	Pre	Post	p
Hct, %	38.5	41.9	0.04	33.8	36.6	0.02
Na, mmol/L	139	138	0.66	136	136	0.74
K, mmol/L	4.4	3.7	0.08	4.4	4.2	0.10
GLC, mg/dL	154	137	0.31	97	131	0.19
Ca, mg/dL	8.7	8.7	0.87	9.3	8.6	0.13
Crt, mg/dL	0.6	0.6	1.00	0.4	0.4	1.00

Table 3. Comparison of Changes in Laboratory Values After CPD/A vs. AS1/3 Transfusion

	CPD/A (Δ)	AS1/3 (Δ)	p
Hct, %	3.4	2.8	0.37
Na, mmol/L	-0.7	-0.5	0.93
K, mmol/L	-0.7	-0.2	0.14
GLC, mg/dL	-17	34	0.08
Ca, mg/dL	0.05	-0.7	0.08
Crt, mg/dL	0	0	0.20

Results

Four infants received 6 CPD/A units; four infants received 6 AS1/3 units (*Table 1*). Hematocrit was significantly increased after transfusion of CPD/A (p=0.04) or AS1/3 (p=0.02) units, with mean differences of 3.4% after CPD/A and 2.8% after AS1/3 transfusions (p, NS)(*Table 2,3*). No other statistically significant differences between pre- and post-transfusion laboratory values were observed (*Table 2*).

Mean differences in serum chemistry values (D) following CPD/A or AS1/3 transfusion were compared (*Table 3*). These changes observed in laboratory values following transfusion of CPD/A or AS1/3 units were not statistically or clinically significant. No adverse reactions to blood transfusion were reported.

Conclusions

Transfusion of AS1/3 units appears to be tolerated as well as CPD/A units by infants on ECMO, suggesting removal of AS supernatant or washing is unnecessary. The data support less reliance on CPD/A units for infants, an important consideration in light of the decreasing availability and greater expense of these units compared to AS units. The data also support simplification of transfusion protocols at our institution, eliminating the need for a separate inventory of CPD/A units or further manipulation of red cell units for infants on ECMO.

Comparison of CPDA vs AS Red Cell Transfusion to Infants on ECMO

- **Purpose: Transfusion protocols were developed for infants on ECMO in the absence of definitive evidence to guide clinical decisions.**
- **Practices vary among pediatric institutions with respect to:**
  - **Selection of red cell components.**
  - **Maximum storage time before transfusion.**
  - **Additive solution/anticoagulant preservative used.**
  - **Further modification to the units (washing, supernatant removal, etc)**

Comparison of CPDA vs AS Red Cell Transfusion to Infants on ECMO

- Retrospective audit included 4 infants receiving 6 CPD/A units and 4 infants receiving 6 AS-1/3 units. (Both groups received whole red cell transfusions)
  - Study compared pre & 4 hour post transfusion values for Hct, Na, K+, Ca, Glucose, and Creatinine.
  - Study results: Hct increased significantly after CPD/A(mean difference 3.4%) RBC transfusion compared to AS-1/3(mean difference 2.8%) RBC transfusion.
  - No other statistically significant differences between pre and post transfusion laboratory values were observed.

Eder et el, Children's Hospital of Philadelphia, Comparison of CPDA vs AS Red Cell Transfusion to Infants on Ecmo

Current Conclusions (1)

- **Commentary on the Safety of Red Cells Preserved in Extended Storage Media for Neonatal Transfusions.**
  - **Amount of additive solution transfused to during small volume transfusion settings was far below the toxic dose.**
  - **Several complicating factors to accurately estimate the toxic dose of additive solution transfused neonates to during large volume transfusion.**
- **Clinical studies in support of small volume transfusion with additive RBC's.**
  - **Review of six clinical studies shows no evidence of adverse consequences or significant differences in blood chemistries**

Current Conclusions (2)

- **University Health Consortium Survey of blood component preferences for transfusion services.**
  - **Included questions concerning use of AS for low volume neonatal transfusion (<20ml/kg)**
  - **Survey results indicated that the majority of transfusions services were willing to use at least one additive solution.**
  - **Many respondents indicated the willingness to use all three additive solutions.**
- **Comparison of 4 neonates receiving 6 CPD/A vs 4 neonates receiving 6 AS1/3 whole unit transfusions.**
  - **No statistically significant differences between pre and post transfusion laboratory values except Hct%.**

Survey of the Use of Red Cell Additive Solutions & Special Attributes in Neonatal Patients

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1. SSM Health Cardinal Glennon Children's Hospital, St Louis, MO

2. American Red Cross, Durham, NC

3. Blood Works Northwest, Seattle, WA

4. University of Washington, Department of Laboratory Medicine & Pediatrics, Seattle, WA

SSMHealth CardinalGlennon Children's Hospital

Bloodworks Northwest

American Red Cross

Survey Goal

Assess the transfusion practice for neonatal patients at a subset of institutions concerning:

- **1: RBC additive of choice in a variety of clinical settings, including additional modifications**
- **2: Policies concerning CMV seronegative blood products**
- **3: Policies concerning Irradiated blood products**

Methods

- **Survey: 78 facilities throughout the U.S.A.**
  - **21 centers participated (27% response rate)**

- **Definitions**
  - **Neonates: <4months of age**
  - **Small volume transfusion: <20mL/kg**
  - **Large volume transfusion: ≥20 mL/kg**

Responding Centers' Demographics

- 24% - pediatric only.
- 76% - adult & pediatric.
- Average NICU bed size was 81 beds.
- 90.5% identified as academic facilities

Results, Use of AS-1 & AS-3 in Small and Large Volume Neonatal Transfusion

RBC Dose	CPD	CPDA	AS-1	AS-3	AS-5
Small Volume Transfusion (<20mL/kg)	14%	14%	24%	38%	0%
Large Volume Transfusion (>20mL/kg)	14%	14%	29%	43%	0%

*** n = 21**

72% (15 of 21 centers)

Results, Additional Modifications for AS RBCs in Large Volume Transfusion Settings

Clinical setting	Fresh (<7-10 d)	Washed	Supernatant Reduced	No Modification
General Surgery n=13	61%	8%	8%	23%

Results, Additional Modifications for AS RBCs in Large Volume Transfusion Settings

Clinical setting	Fresh (<7 – 10 d)	Washed	Supernatant Reduced	No Modification
General Surgery n=13	61%	8%	8%	23%
Cardiac Surgery n=12	75%	8%	0%	17%

Results, Additional Modifications for AS RBCs in Large Volume Transfusion Settings

Clinical setting	Fresh (<7 – 10 d)	Washed	Supernatant Reduced	No Modification
General Surgery n=13	61%	8%	8%	23%
Cardiac Surgery n=12	75%	8%	0%	17%
ABO Incompatible Heart Transplant n=7	29%	43%	14%	14%

Results, Additional Modifications for AS RBCs in Large Volume Transfusion Settings

Clinical setting	Fresh (<7 – 10 d)	Washed	Supernatant Reduced	No Modification
General Surgery n=13	61%	8%	8%	23%
Cardiac Surgery n=12	75%	8%	0%	17%
ABO Incompatible Heart Transplant n=7	29%	43%	14%	14%
Extra Corporeal Life Support n=10	80%	10%	0%	10%

Results, Additional Modifications for AS RBCs in Large Volume Transfusion Settings

Clinical setting	Fresh (<7 – 10 d)	Washed	Supernatant Reduced	No Modification
General Surgery n=13	61%	8%	8%	23%
Cardiac Surgery n=12	75%	8%	0%	17%
ABO Incompatible Heart Transplant n=7	29%	43%	14%	14%
Extra Corporeal Life Support n=10	80%	10%	0%	10%
Exchange Transfusion n=13	69%	15%	8%	8%

Survey Conclusions

- **A majority (72%) of respondents have transitioned to the use of AS-1 or AS-3 for large volume neonatal transfusions in a variety of clinical settings.**
  - **The use of AS units appears widely accepted in large volume transfusion, even though there are not clinical studies to support the practice.**
- **Many respondents choose fresh RBC products, possibly due to the risk of transfusion associated hyperkalemia, although the reason for the fresh product was not investigated**
- **The survey does not provide a guidance for practice, but offers a snapshot of practice.**
- **Further research into the best product parameters for large volume neonatal transfusion are needed.**

Thank You

Questions?

A Word About RBC Product Processing

	All Neonates	Case-By-Case Basis	Not Available and Not Provided
CMV Seronegative	26%	21%	**47%**
Leukocyte Reduced	**100%**	0%	0%
Irradiated	**89%**	11%	0%

*** n = 19**

Current Practice for Prevention of Transfusion Transmitted CMV Infection in the United States

- **Common methods to avoid TT-CMV infection**
  - **Transfuse leukocyte reduced CMV seronegative RBC units**
  - **Transfuse leukocyte reduced RBC units**
- **Wide variety of practices for the provision of CMV-safe blood products**
- **No uniform practice for specific patient populations among institutions.**
- **Academic institutions were more likely to believe that leukocyte reduced blood products are equivalent to CMV seronegative blood products.**

Smith et al, *Vox Sanguinis*, 2010