New York Blood Center Enterprises

What hath the Europeans wrought?

Potential Elimination of CPDA-1

Eric Senaldi, MD

Introduction

- Over decades FDA has approved many additive solutions to extend the shelf life of RBCs in the presence of reduced amount of plasma.

Objectives

- Overview of DEHP free blood bags
- Review of literature for additive solution rbc use in neonatal transfusion
- National Surveys of pediatric and neonatal transfusion

Conclusions

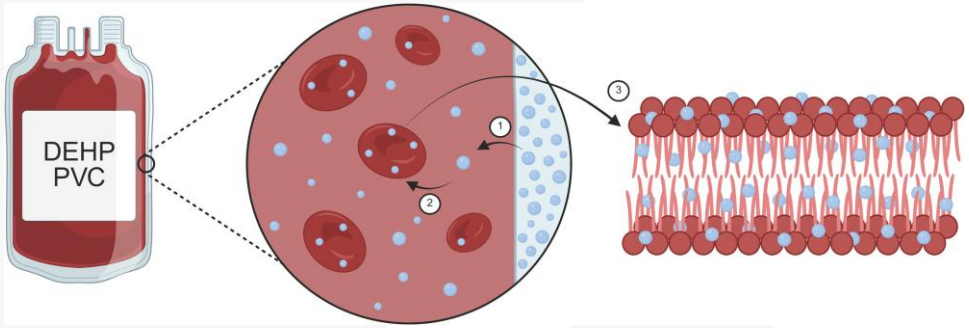
- There is neither literature to support superiority of one solution over the other; nor is there a data to show detrimental effects of any of these in neonates.
- Change is the only constant.

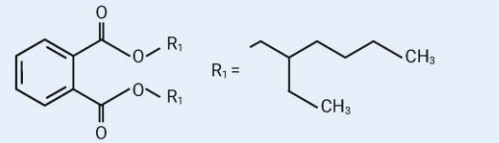
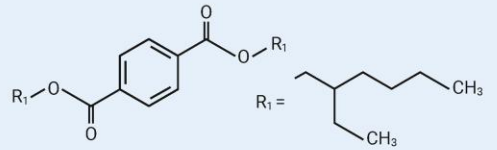
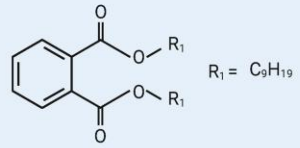
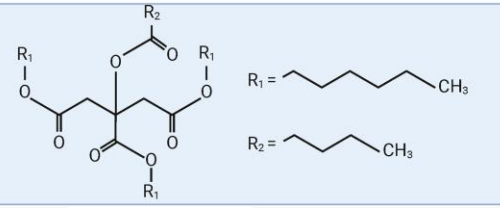
Why is DEHP in Medical Plastics

- DEHP – di(2-ethylhexyl) phthalate
  - Ubiquitous in the environment, ingest, inhale, absorb it
  - Broken down in the liver, excreted in feces and urine within 24 hours
- Primary plasticizer to make polyvinyl chloride (PVC) storage bags flexible
  - Increased durability and flexibility
  - Minimize risk of breakage
  - Enable steam sterilization & freezing
- Problem
  - Lipophilic and dipolar
  - Non-covalent binding to PVC
  - Leaches into blood components
  - Animal studies show reproductive and developmental toxicity
  - Ambiguous evidence of potential human adverse effects – endocrine disruptor
  - Androgen antagonist and estrogen agonist
- Tolerable daily intake 48ug/kg body weight based on no observed adverse events
  - 1 rbc transfusion can exceed twice the that limit

Why Can't We Remove It?

- DEHP incorporates into RBC phospholipid bilayer
  - Stabilizes membrane
  - Reduces hemolysis
  - Limits microvesicle formation
  - Maintain osmotic stability
- Alternative compounds:
  - DEHT – Toys and consumer products
  - DINCH – Food packaging and platelet storage bags
  - BTHC – Platelet storage bags
- Problems
    - Higher hemolysis rate
    - Reduced recovery
    - Effects of irradiation and freezing are not well known
  - Benefits
    - Less leaching into component
    - Higher tolerable intake



Plasticizer	Formula
Di(2-ethylhexyl) phthalate (DEHP)	
Di(2-ethylhexyl) terephthalate (DEHT)	
1,2-cyclohexane dicarboxylic acid diisononyl ester (DINCH)	
N-butyryl-n-hexyl citrate (BTHC)	

You Don’t Get Something for Nothing

- European Medical Device Regulation wants a full phase-out of DEHP by July 2030
- Next generation additive solutions to replace AS-1 and SAGM (Europe) are necessary to meet EU and FDA requirements.
- PAGGSM or PAGGGM, not licensed in US
- All additive solutions except AS-3 have mannitol to help stabilize the rbc membrane
  - DEHT-PAGGSM, DINCH-AS-3, DINCH-PAGGSM, and BTHC-PAGGSM met European and FDA criteria
  - DEHT-AS-1 barely met European standards for hemolysis
  - DINCH-SAGM, and BTHC-SAGM did not meet European hemolysis standards

Overview of the most commonly used additive solutions for red cell concentrates.

	Europe			United States/Canada			
Ingredients	SAGM	PAGGSM	PAGGGM[a]	AS-1	AS-3	AS-5	AS-7
NaCl (mmol/L)	150	72		154	70	150	
Na_2HPO_4 (mmol/L)		16	8				12
$NaHCO_3$ (mmol/L)							26
NaH_2PO_4 (mmol/L)		8	8		15.5		
Citric acid (mmol/L)					2		
Na-citrate (mmol/L)					20		
Adenine (mmol/L)	1.25	1.4	1.4	2	2	2.2	2
Guanosine (mmol/L)		1.4	1.4				
Glucose (mmol/L)		47	47	111	61		80
Dextrose anhydrous (mmol/L)	41					41	
Na-gluconate (mmol/L)			40				
Mannitol (mmol/L)	30	55	55	41		45.5	55
pH	5.7	5.7	8.2	5.5	5.5	5.5	8.5
Osmolarity (MOsm/L)	376	345	275	462	291	372	237

Abbreviations: AS, additive solution; PAGGGM, phosphate-adenine-glucose-guanosine-gluconate-mannitol; PAGGSM, phosphate-adenine-glucose-guanosine-saline-mannitol; SAGM, saline-adenine-glucose-mannitol.
[a] Experimental additive solution.

Van Wonderen SF. et al
https://doi.org/10.1016/j.tmrv.2025.150904
Van Wonderen SF. et al Vox Sang 2026 Feb 10
https://doi.org/10.1111/vox.70213

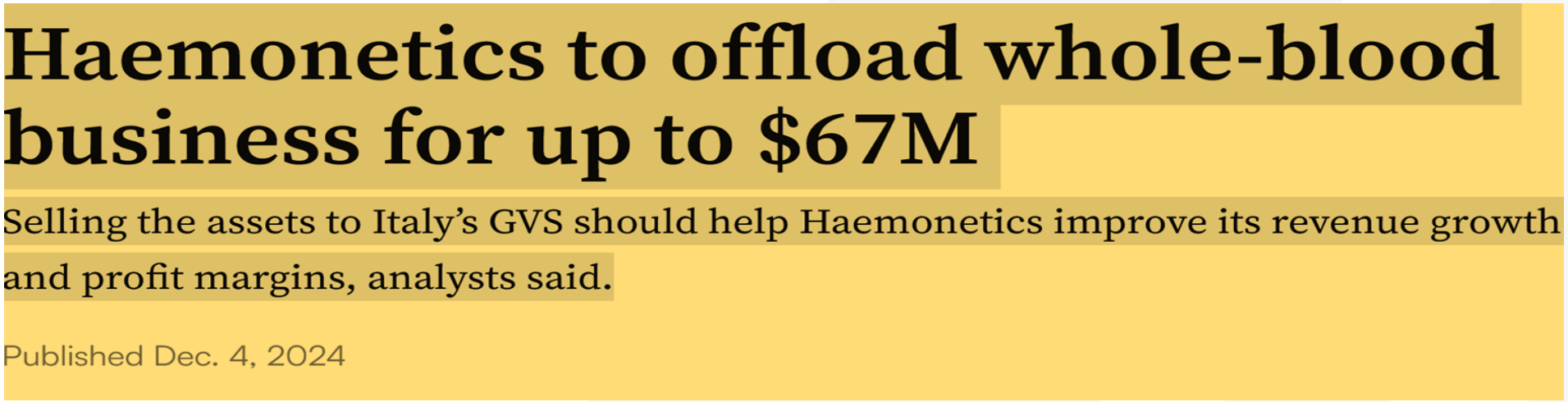
Regulatory Issues

- Current standards
  - European Standards < 0.8% hemolysis at the end of storage
  - FDA standards – 75% in-vivo recovery at 24 hours in 24 volunteers
    - For validating new additive solutions but unknown if they apply to different plastics
- Europeans further along with alliances among the stakeholders
  - Blood centers, hospitals, manufacturers
  - No guidance on what data is necessary for safety or efficacy
- Probable requirements – bag manufacturers need to define with regulators
  - Pre-market laboratory data
  - Pre-market clinical data
  - Post market surveillance
  - Data for blood collection & transformation – irradiation, freezing, washing, pathogen reduction
  - Need to decide which components to focus on – all or only rbc – plasma & platelets – no effects
- How much and what data can be based on post market surveillance
  - Hospitals & blood centers– recovery, survival, allergic reactions, bag failure
  - Whatever is measured needs a control – need to measure current bags and AS prior to new measuring new
- Will whole blood react the same as components to new plastics
  - No additive solution
  - Shorter expiration dates

Brown, B et al Transfusion 2025;65:2414-2422

What's Happening with our Current Blood Bags

- Fresenius Kabi, current supplier of CPDA-1, will stop production of the bags by the end of year 2026 or first quarter 2027 –
  - Bag and anticoagulant not in widespread use in Europe
  - Current plastic is DEHP – not planning to change to DEHP free – probably would not meet FDA criteria



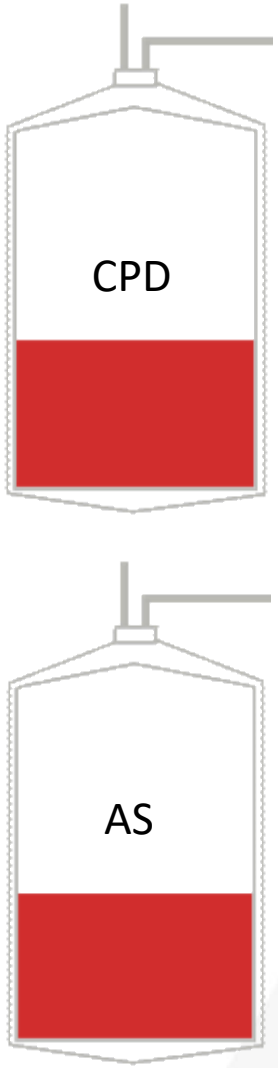
Haemonetics to offload whole-blood business for up to $67M

Selling the assets to Italy's GVS should help Haemonetics improve its revenue growth and profit margins, analysts said.

Published Dec. 4, 2024

- Haemonetics – maker of bag set with AS-3 anticoagulant sold the business in 2025. The new owner, GVS, has yet to receive approval to begin production.
- Trima Accel apheresis red blood cells are in AS-3 but availability is limited
- European bags use a top and bottom bag (FDA unlicensed) as opposed to the US – this requires a change in the component manufacturing process in US blood centers

What's in the bag?



- 225-300 mL RBCs
- Residual plasma
- No additive solution
- Hct: 65-85%

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

Circular of Information for the use of Human Blood and Blood components. October 2017. Table 1&2. Pages 13-14

Additive Solution vs CPD Solution

Constituent	CPDA	AS-1	AS-3	AS-5
Volume (mL)	63	100	100	100
NaCl (mg)	None	900	410	877
Dextrose (mg)	2000	2200	1100	900
Adenine (mg)	17.3	27	30	30
Mannitol (mg)	NONE	750	NONE	525
Tri-sodium citrate (mg)	1660	None	588	None
Citric Acid (mg)	206	None	42	None
$NaPO_4$ (mg)	140	None	276	None

- As noted from the table; AS-1 and AS-5 have a similar composition.
- It proves to have a similar safety profile.
- For all the studies referring to AS-1, data can be extrapolated to AS-5.

Strauss RG(1). Transfusion. 2000 Dec;40(12):1528-40

Pediatrician Concerns

- Glucose- Concern with AS > CPDA-1 (hyperglycemia can cause hyperinsulinemia and prolonged rebound hypoglycemia)
- Adenine- Glomerulosclerosis (Nephrotoxicity)
- Hypernatremia
  - ↑ BP, edema
  - Renal failure,
  - Brain shrinkage leading to IVH
- Mannitol in AS-1 and AS-5 (Osmotic Diuresis)
  - Fluid Shift
  - Headaches
  - Intracranial Bleed
  - Nephrotoxicity
- Hypocalcemia- From high citrate and phosphate in AS-3 Units

Study 1- Comparison of two preservation solutions for erythrocyte transfusions in newborn infants

- Low Birth Weight Infants (n-16, 31 transfusions)
- RBC- 17ml/kg, AS-1 and CPDA-1
- Randomized cross over study
- Pre(1hr) and post(1 and 4hrs) transfusion lab parameters
- Effective increase in Hb noted with both products
- No significant difference in biochemical panel between the two cohorts
- Mild subclinical ammonia increase was noted in both arms till 4 hours
- Drop in blood glucose level was slow with AS- RBC

•Goldstein MH et al.1993 Nov;123(5):783-8. doi: 10.1016/s0022-3476(05)80860-1

Study 2: AS-1 red cells for neonatal transfusions: a randomized trial assessing donor exposure and safety

- Premature Infants
- Randomized single blind study
- Dose- 15ml/hr transfused over 5 hours
- AS-1 (42 days) VS CPDA-1 (≤ 7 days)
- Primary Endpoint: RBC's from a single donor (AS-1) could safely supply all small volume transfusions with in first 84 days of life
- Secondary Endpoint: Assess adverse clinical and biochemical effects with AS-1 units
- Results

  Mean Units exposed: AS-1 (1.6) vs CPDA-1 (3.7), $P < 0.05$

  No Significant difference in clinical or biochemical events

Straus RG et al, Transfusion 1996

Neonatologist Concerns – RBC age

- No significant differences when neonates are transfused <7 days vs >14 days old RBCs
- ARIPI - rbc age in premature infants randomized controlled trial
  - Outcomes measured: necrotizing enterocolitis, retinopathy of prematurity, bronchopulmonary dysplasia, and intraventricular hemorrhage, death.
  - No difference in outcomes in premature VLBW infants requiring a transfusion; fresh RBCs (mean age 5.1 days) vs standard blood bank practices (mean age 14.6 days)
  - *Fergusson DA et al. JAMA. 2012 Oct 10;308(14):1443-51*
- TOTAL - randomized clinical trial: 290 children aged 6- 60 months old
  - Short storage(median age=8 days) vs long storage (median age=32 days)
  - Children with severe anemia and elevated lactate levels
  - Compare the post transfusion correction of mean lactate levels
  - No difference in the two arms - fresh vs old blood
  - *Dhabangi JAMA. 2015 Dec 15;314(23):2514-23.*
- Similarly INFORM, ABLE and RECESS trial in adults have shown no advantage of fresh blood over the extended storage blood

NEONATOLOGIST CONCERNS – HYPERKALEMIA

- Older AS-1 RBCs ≠ Potassium overload

Daily K^+ requirement	K^+ levels in RBC at end of 42 days storage in AS-1	Slow transfusion of 15 mL/kg of AS-1 RBCs stored at Hct=55% to an infant of 1 kg
2-3 mEq/kg	0.05mEq/mL (but bioavailable extracellular ionic K^+ is very small)	0.3 mEq of K^+

- K^+ doses are quite small when compared to daily requirement and have been shown in several clinical studies not to cause hyperkalemia
  - *Strauss RG(1). Transfusion. 2008 Feb;48(2):209-17*
- *Hume* in a systematic review of 4 studies - no correlation between hyperkalemia and age of RBCs stored.
  - *Hume H(1). Semin Perinatol. 1997 Feb;21(1):8-19.*
- No significant pre and post transfusion K+ level changes were noted even when the RBCs were not washed or supernatant fluid removed.
  - *Liu EA et al. J Pediatr. 1994 Jul;125(1):92-6.*
- Studies have shown that K+ levels of irradiated AS-1 stored for 28 days is lower compared to levels in 14 days storage in CPDA1 or AS-3 due to protective effect of Mannitol
  - *El Kenz H(1). Transfus Apher Sci. 2013 Oct;49(2):249-53*
- No correlation with unit age or unit K+ concentration was identified with change in patient whole-blood K+ concentration. The lack of clinical effect on patient potassium does not support the use of “fresh” pRBC units with routine pediatric transfusion.
  - *Jordan Olson. AJCP Volume 139, Issue 6, 1 June 2013 pages 800-805*

Neonatologist Concerns – Hyperkalemia

- Many clinical trials have established the safety of AS-1 red cells of any age in a small volume transfusion
- There are only anecdotal data regarding RBCs stored in additives for large volume transfusions and the benefits of washed RBCs
- The following recommendation for large volume transfusion @ 25ml/kg during an emergency is not based on results of clinical trials investigating rapid infusion RBC emergency transfusions, because they do not exist, but per calculations.
  - After 20 days of storage of RBCs in AS-1 (average age of RBC in an inventory); RBC transfusion @ 0.5 mL/Kg/min leads to K+ infusion @ 0.007 mEq/Kg/min which is not greatly different from the dose of replacement rate of K+ in hypokalemic patients of 0.004 mEq/Kg/min
- Thus in grave bleeding situations, the potential risk of infusing potassium at a rate slightly higher than rates accepted to be safe seems reasonable. The practice of limiting RBC infusion rates is analogous to limitations followed to avoid toxicity of drugs infused intravenously.
  - *Strauss RG. Transfusion. 2010;50(9):1862-1865*

Neonatologist Concerns – Donor Exposures

- In infants, mean donor exposure was 1.6 (AS-RBCs) vs 3.7 (CPDA1 RBCs).
- *Strauss RG et al. Transfusion. 1996 Oct;36(10):873-8*

- Increased Shelf life and Decreased donor exposure
  - Aliquots from a single dedicated donor unit (AS-1 preserved) can be allotted to a neonate.
  - Hence, 64% reduced donor exposure with transfusion of AS-1 RBCs compared to providing fresh (<7 days old) CPDA1 RBCs.
- *Lee DA et al. J Pediatr. 1995 Feb;126(2):280-6*

Neonatologist Concerns – Safety of Additive Solutions

- The doses of constituents of AS-1 and AS-3 solutions are far below the toxicity doses
  - *Strauss RG. Transfusion. 2000 Dec;40(12):1528-40*

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	5.6	>60 mg/kg/day
Mannitol	33	33	>60 mg/kg/day

Adenine levels in	
Small volume transfusion (15ml/kg)	0.7mg/kg
Exchange transfusion	2.6mg/kg
Nephrotoxicity levels	95mg/kg when cumulatively transfused in a 5 day period

- Small volume transfusion,adenine dose does not approach a significant levels to cause renal toxicity.
- Adenine is added to RBCs to maintain the cell shape and viability.
- As adenine rapidly enters the RBCs and becomes converted to ATP the bioavailability after transfusion is reduced.
  - *Luban NL(1). Transfusion. 1991 Mar-Apr;31(3):229-35.*

Neonatologist Concerns – Safety of Additive Solutions Mannitol

- Mannitol is a membrane stabilizer that helps reduce hemolysis during storage.
- Route of excretion: Kidneys; T1/2= 100 minutes.
- High mannitol volume – used as an osmotic diuretic 250-500mg/kg may lead to :
  - Shift in intravascular volume affecting cerebral blood flow
  - Fluid imbalances
  - Increased serum osmolality
  - Electrolyte disturbance
  - Affects brain, heart and kidney functions

Dose of mannitol for treatment of cerebral edema in children of all age (WHO model formulary for children 2008)	Renal Toxicity levels	Dose of mannitol in AS-1 RBC for Small volume transfusion **(15ml/kg)**
200 mg/kg	360-720 mg/kg	22-33mg/kg (1/10th the toxicity levels)

- Neonatal transfusion - 8 fold or more less than dosage as osmotic diuretic
  - 10-20ml/kg = 15-60mg/kg mannitol
- Hence, even neonates receiving frequent small volume transfusion will have no significant effects
  - *Luban NL. Transfusion. 1991 Mar-Apr;31(3):229-35.*
  - *Strauss RG(1). Transfusion. 2000 Dec;40(12):1528-40.*

Alternatives for Large Volume/High Flow Situations

- High volume / high blood transfusion rate >30ml/kg/hr
  - Extreme low birthweight or intrauterine transfusions
  - Mitigation through washing or volume reduction of supernatant
    - Delay in transfusion
    - Impact quality and volume of the rbc – mechanical damage, fragility
    - Impractical in emergencies
- Clinical decision based on patient clinical status
  - Which risk is greater: Delaying transfusion or mannitol & high volume/rate

BLOOD CHEMISTRY

- No significant differences in pre and post transfusion blood chemistries with different additive solutions
- With small volume transfusion (15 ml/kg), no evidence of risk of
  - Hyperglycemia
  - Hypocalcemia
  - Hypernatremia

Table 4. *Changes (delta values) in blood chemistry analyses from pretransfusion values to posttransfusion values**

Variables	CPDA-1 RBCs transfused† (n = 67-79)		AS-1 RBCs transfused† (n = 60-74)		p values
Hct (%)	12 ± 4	(12)	12 ± 5	(11)	0.34
Glucose (mg/dL)	–9 ± 32	(–8)	–7 ± 25	(–8)	0.52
Lactate (mmol/L)	–0.3 ± 0.4	(–3.0)	–0.1 ± 0.6	(–1.0)	0.26
pH	0.00 ± 0.05	(0.01)	0.00 ± 0.13	(–0.02)	0.78
Calcium (mg/dL)	–0.1 ± 0.7	(0.2)	–0.1 ± 0.5	(0.1)	0.66
Sodium (mEq/L)	0.5 ± 4.4	(0.5)	0.6 ± 5.1	(1.0)	0.24
Potassium (mEq/L)	0.3 ± 0.9	(0.3)	–0.2 ± 1.5	(–0.1)	0.16

- Strauss RG. Transfusion. 1996 Oct;36(10):873-8

TRANSFUSION REACTIONS

- No significant differences in rate of transfusion reactions with different additive solutions
- Pre and post transfusion changes in vital sign were not clinically significant

Table 3. *Clinical reactions and changes in vital signs observed in 29 infants given 124 RBC transfusions*

	CPDA-1 RBCs transfused		AS-1 RBCs transfused		
	Infants	Transfusions	Infants	Transfusions	p values*
Infants or transfusions	15	58	14	66	1.00
Transfusion reaction noted	0	0	0	0	NT
Temperature rose >1°C	1	1	0	0	1.00
Pulse rose >30 beats/minute	4	5	6	7	0.45
Systolic blood pressure rose >20 torr	5	6	6	9	0.71
≥2 vital signs altered	1	1	0	0	1.00

- Strauss RG(1). Transfusion. 1996 Oct;36(10):873-8.

NEONATAL TRANSFUSION Changing Literature - Early

- Most RBC transfusions are given to preterm infants.
- Small Volume transfusion:
  - Dose: 10-20 mL/kg slowly over 2-4 hours.
  - Type of preservative solution poses no risk to the neonate.
  - Recommendations: No additional processing required
- Large Volume Transfusion (eg: ECMO, RBC exchange for hyperbilirubinemia)
  - Dose: (>25 ml/kg); At least equivalent to one circulating blood volume (80ml/kg over 24 hours) or 50% circulating volume in 3 hour.
- For large volume transfusion - Human model was studied with hypothetical settings and calculations – overestimate at 80ml/kg and underestimate at one blood volume
- Conclusion
  - It was impossible to estimate accurately the degree of exposure considering variables such as the clinical setting, duration of exposure to additive solutions, bioavailability of solutes, intracellular trapping of solutes and dispersion to extracellular compartments of solutes, combined with the patient's renal and hepatic status all complicate toxic dose calculations
- Recommendations based on these Hypothetical calculations was to provide washed RBCs or fresh RBCs
  - Luban Et al Transfusion. 1991 Mar-Apr;31(3):229-35

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 (Δ) 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 arteries	3	B		
4	C			4	E	3m	Bridge to lung transplant
5	D	2d	Cardiac arrest, congenital heart disease	5	E		
6	D			6	F	5d	Transposition of the great arteries, double outlet right ventricle ap 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 unit (*Table 1*). Hematocrit was significantly increased after transfusion of CPD/ (p=0.04) or AS1/3 (p=0.02) units, with mean differences of 3.4% afte CPD/A and 2.8% after AS1/3 transfusions (p, NS)(*Table 2,3*). No oth statistically significant differences between pre- and post-transfusio laboratory values were observed (*Table 2*).

Mean differences in serum chemistry values (Δ) following CPD/A or AS1, transfusion were compared (*Table 3*). These changes observed laboratory values following transfusion of CPD/A or AS1/3 units were n statistically or clinically significant. No adverse reactions to bloc transfusion were reported.

Conclusions

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

Eder et al. Children's Hospital of Philadelphia. Comparison of CPDA vs. Red Cell Transfusion To infants on ECMO. Department of Pathology and Laboratory Medicine

10 years later; NEONATAL large volume transfusion Eder et al CPDA vs. AS

- Comparison of CPDA-1 vs AS-1 RBCs in infants on ECMO
- Retrospective audit included 4 infants receiving 6 CPD/A units and 4 infants receiving 6 AS-1/3 units.
- Study compared pre & 4 hour post transfusion values for Hct, Na, K+, Ca, Glucose, and Creatinine.
- 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 significant difference in blood chemistries were identified in these two groups.
- No adverse reactions to blood products
- Transfusion of AS1 and AS-3 units appear to be tolerated as well as CPD/A units by infants on ECMO, suggesting removal of AS supernatant or washing is unnecessary.
  - *Eder, AF & Gray, K & Manno, CS. (2002). Comparison of CPDA with AS red cell transfusion to infants undergoing ECMO.*

Supportive animal model studies

- Animal model for large volume transfusion involved transfusing 20 units of CPDA-1 whole blood or 20 units of AS-1 RBCs over a period of 90 minutes in each arm.
- The effect of mannitol (osmotic diuresis), glucose and citrate were monitored
- Results/conclusions
  - No significant difference in urine output in animals given Adsol vs CPDA-1 RBCs
  - Mannitol in Adsol appears unlikely to be a cause for concern, even when large volume transfusion are administered.

  - Buchholz DH(1). Transfusion. 1999 Sep;39(9):998-1004.

CHANGING TRENDS IN TRANSFUSION PRACTICES 1993

- Levy GJ et al. National survey of neonatal transfusion practices: I. Red blood cell therapy.
  - Pediatrics. Mar 1993;91(3):523-9 1993
- Survey involved 452 participating institutions (45% Academic centers and 43% primary pediatric hospitals without medical school affiliation)
- Results
  - 70% preferred CPDA and 18% transfused AS-1 RBCs
  - Blood Products selected for transfusion 73% unmodified and 13% washed

CHANGING TRENDS IN TRANSFUSION PRACTICES 2010

- University healthsystem consortium, benchmarking study.
  - Fung et al. Transfusion Volume 50, Issue 9 September 2010 Pages 1921-1925
- 47 respondents across from academic settings and community hospitals
- Results
  - 60% accepted use of at least one (AS-1, AS-3 or AS-5)
  - 45% accepted the use of all three additive solutions
  - 82% no policy for washing after irradiation

CHANGING TRENDS IN TRANSFUSION PRACTICES 2017

- Survey across US about neonatal large volume transfusion practices:
  - 21/78 responded.
- Choice of Additive Solutions
  - AS-3= 43%
  - AS-1= 29%
  - CP2D or CPDA-1= 28%
- A large proportion of centers provide fresh AS RBCs (<10 days was old considered the median of responding centers).
- Modifications of AS units is an infrequent practice.
  - Highest proportion of washed RBCs was given in ABO incompatible heart transplant to remove isohemagglutinins.

Clinical setting of large volume transfusion	Fresh (%)	Washed (%)	Supernatant reduced (%)	No modifications (%)
General surgey (n=13)	61	8	8	23
Cardiac surgery (n-12)	75	8	0	17
ABO incompatible heart transplant (n=7)	29	43	14	14
Extracoporeal life support (n=10)	80	10	0	10
Exchange transfusion (n=13)	69	15	8	8

- Pyles, R., Lowery, J. and Delaney, M. May 2017 ISBT Science Series 12(2) DOI:10.1111/voxs.12343

CHANGING TRENDS IN TRANSFUSION PRACTICES 2021

RBC Anticoagulant by Patient Age & Volume of Transfusion

- Survey of 35 institutions
- 40% Academic pediatric hospital
- 31% Academic adult and pediatric
- 26% Community hospital
- 90% had NICU or PICU or both
- 58% Pediatric Level 1 trauma
- 63% ECMO
- Definitions
  - Neonate 0-4 months (NEO)
  - Pediatric > 4 months (PED)
  - Small volume <20ml/kg (SV)
  - Large volume >20ml/kg (LV)
- Question: Select all that apply
- 2 institutions wash or remove AS for neonatal use for all transfusions

Anticoagulant % by Patient and Transfusion

Type	CPDA CPD CP2D	AS-1	AS-3	AS-5	AS-7
SV – NEO	34%	18.3%	21.5%	17.2%	2.6%
LV-NEO	34.5%	17.9%	21.4%	17.9%	1.2%
SV-PED	24.8%	26.7%	23.8%	17.8%	2%
LV-PED	26.2%	26.2%	24.3%	17.5%	1.9%

Reeves HM et al, Transfusion 2021;61:2265-2276
https://doi.org/10.1111/trf.16520

Other Findings from 2021 Survey

- >60% institutions had policy for storage age of rbcs for neonatal SV & LV
  - Range from 5-14 days – no uniform definition
- >70% institutions had no policy for storage age of rbcs for pediatric SV & LV
- ABO/Rh
  - Neonatal non-urgent
    - 74% Group O, 23% Rh neg, 48% Rh compatible, 3% Rh neg for all female
    - 26% - use ABO/Rh compatible
  - Pediatric non-urgent – 97% ABO/Rh compatible
- Washing units
  - 60% and 72% sometimes wash units for patients - hyperkalemia or history of transfusion reactions

Reeves HM et al, Transfusion2021;61:2265-2276
https://doi.org/10.1111/trf.16520

Conclusions

- Neonatal transfusion practices are variable but the trend is changing; from moving away from No Additive solutions to Additive solutions with only 1/3 of institutions surveyed using non-additive solutions
- Components of the additive solutions given during small volume transfusion do not approach toxicity levels.
- No difference in transfusion reactions or blood chemistries with use of CPDA, AS-1, AS-3, or AS-5 RBCs
- Additive solutions like AS-1, AS-3 or AS-5 help reducing the number of donor exposures in infants.
- Moreover, there are no definitive data to establish superior efficacy and/or safety of RBCs stored in CPD or CPDA solutions - the ones often demanded by neonatologists - over RBCs in additive solutions for small volume transfusions
- Overall, the additive solutions are safe and well tolerated by premature infants to a level of 30ml/kg/hr

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