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BLOOD BULLETIN

Neonatal Transfusion Support - Modifications and Preparations of Red Cell Transfusions — A Case Study

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KEY POINTS

- This *Blood Bulletin* examines key considerations for neonatal red blood cell (RBC) transfusions through a case study of a preterm infant with severe hypovolemic shock requiring high-volume transfusion (>20 mL/kg of RBCs).
- Topics include considerations of specific RBC product modifications and preparations in high-volume transfusions, such as potassium load management, preservative solutions, and unit storage length.
- Additionally, cytomegalovirus (CMV) transmission risk and hemoglobin S (HbS) screening is discussed.
- The goal is to provide evidence-based guidance for optimizing RBC transfusion practices in neonatal scenarios.

CASE STUDY

Part I. A male neonate weighing 1 kilogram was emergently delivered at 31 weeks of gestation in a local community hospital after antenatal detection of fetal heart rate decelerations and cardiac anomalies on ultrasound. The delivery was further complicated by a significant placental hemorrhage.

At birth, the neonate exhibited severe pallor, poor peripheral perfusion, and signs of profound hemodynamic instability. Initial assessments revealed the following:

- **Apgar Scores:** 2 at 1 minute, 5 at 5 minutes;
- **Heart Rate:** 180 bpm (severe tachycardia);
- **Respiratory Rate:** 70 breaths per minute (tachypnea);
- **Blood Pressure:** 35/20 mmHg (severe hypotension);
- **Hemoglobin:** 6.5 g/dL (critical anemia);
- **Hematocrit:** 19 percent;
- **Arterial Blood Gas:**
  - pH: 7.18 (metabolic acidosis)
  - Base Excess: -12 mEq/L.

INITIAL MANAGEMENT

Resuscitation began immediately with a 10 mL/kg bolus of normal saline to address hypovolemia and hypotension. The attending neonatologist requested an urgent RBC transfusion. The only available unit was a **12-day-old, leukoreduced, O-RhD negative packed RBC (pRBC) preserved in additive solution (AS).** Given the critical condition of the neonate, the transfusion proceeded without prior irradiation or screening for HbS. A high-volume transfusion was indicated due to the neonate's persistent hypotension, severe anemia, and inadequate perfusion despite fluid resuscitation, necessitating the rapid restoration of circulating blood volume and oxygen-carrying capacity; this required transfusion volumes exceeding 20 mL/kg, with the total volume approaching 50–100 mL/kg to stabilize the infant's hemodynamic status.

KEY CONSIDERATIONS

I. How are large volume transfusions defined and what are the risks associated with them in the neonatal setting?

Small-volume (SV) transfusions (<20 mL/kg) are used in neonates to treat moderate anemia or mild hypovolemia. Slower administration (2–5 mL/kg/hour) of small doses (5–15 mL/kg) minimizes risks such as volume overload and electrolyte imbalances. Typically safer, they require less stringent product modifications compared to large-volume transfusions, making them suitable for hemodynamically stable, euvolemic patients. On the other hand, large-volume (LV) transfusions (>20 mL/kg) are used in neonates with severe anemia, blood loss, or shock, often exceeding 50–100 mL/kg in 24 hours. Risks include volume overload, electrolyte imbalances (hyperkalemia, hypocalcemia), coagulopathy, and hypothermia, requiring meticulous monitoring and supportive care.

Clinical Considerations for Small Volume- vs. Large Volume-Transfusions

ASPECT	SMALL VOLUME (<20 ML/KG)	LARGE VOLUME (>20 ML/KG)
Indications	Moderate anemia or mild hypovolemia	Severe anemia, massive blood loss, shock
Delivery Rate	Slower (over 2–4 hours)	Often rapid (emergency settings)
Monitoring	Minimal if stable	Continuous, with focus on hemodynamics
Risks	Minimal	Significant, including circulatory and K+ overload and hypocalcemia
Outcome Goals	Incremental hemoglobin/volume correction	Restoration of perfusion/oxygen delivery

II. Anticoagulant/Preservative Solutions: Additive Solution-Preserved vs. CPD-Preserved Units

Question: How does the safety profile of AS-preserved RBCs compare to anticoagulant citrate-phosphate-dextrose (CPD)-preserved and CPDA-1 (citrate-phosphate-dextrose-adenine) units for high-volume transfusions in neonates?

RBC units stored in AS are safe for SV neonatal transfusions. Evidence for their safety in LV transfusions is less robust. Studies confirm the safety of AS RBCs for SV neonatal transfusion. Two multi-center surveys have examined institutional practices regarding AS RBC use in neonatal transfusions. Reeves et al. reported that institutions accepting AS RBCs for SV transfusion

generally extend the practice to[1] LV neonatal transfusion. A multi-center survey of U.S.-based institutions revealed that a substantial proportion of responding centers utilize AS-containing RBCs for LV- neonatal transfusions, with most taking the product's age into consideration[2].

Comparison of AS (Additive Solutions), CPDA-1, and CPD Preservatives for Neonatal Transfusions

ASPECT	AS (ADDITIVE SOLUTIONS)	CPDA-1 (CITRATE-PHOSPHATE-DEXTROSE-ADENINE)	CPD (CITRATE PHOSPHATE-DEXTROSE)
Pros	Longer RBC storage life (up to 42 days).	Contains no mannitol, reducing the risk of its diuretic and renal effects.	Contains no mannitol, reducing the risk of its diuretic and renal effects.
	May improve blood glucose homeostasis in neonates.	Lower adenine concentration (17.3 mg/63 mL) may pose less risk of renal effects.	No adenine posing less risk of renal effects.
	Provides better red blood cell quality over time.		
	Lower potassium levels during storage, reducing hyperkalemia risk in fresh units.		
Cons	Presence of mannitol (750 mg/100 mL in AS-1) can have diuretic effects.	Shorter storage life for red blood cells (21-35 days).	Shortest storage life for RBCs (21 days).
	Higher adenine levels (27 mg/100 mL in AS-1; 30 mg/100 mL in AS-3) may pose renal toxicity risks.	May not maintain red blood cell quality as effectively over longer periods.	May not maintain RBC quality as effectively over longer periods.
		Higher potassium accumulation in older units, increasing the risk of hyperkalemia.	Higher potassium accumulation in older units, increasing the risk of hyperkalemia.
		Not available from many blood suppliers.	Availability varies by blood supplier.
Safety in Neonates	Shown to be safe for SV transfusions (5-15 mL/kg).	Widely used historically and considered safe, though less optimal for long-term storage.	Used historically and considered safe though less optimal for long-term storage.

III. CMV Transmission Risk

Question: What is the risk of CMV transmission from a leukoreduced blood unit in this setting?

Leukoreduction alone is generally sufficient to prevent transfusion-transmitted CMV (TT-CMV) in neonates. The residual risk of TT-CMV through leukodepleted blood components in Australia is approximately 1 in 13 million overall, which is well below the generally accepted negligible risk threshold for transfusion risks[3]. Delaney et al.'s[4] pilot study demonstrated that leukoreduced blood components were as safe as CMV-seronegative units, with no TT-CMV detected in either group. Breast milk remains the primary source of mother-to-infant postnatal CMV transmission[5].

IV. Consideration of HbS-Negative Units

Question: Is it necessary to provide HbS-negative units of blood in the neonatal setting?

The practice of selecting HbS-negative blood units for neonatal transfusions is common. However, the purported risks of transfusing blood from sickle cell trait (SCT) donors, such as vaso-occlusive events, reduced oxygen delivery, and poor RBC recovery, are based on low-quality evidence[6-8]. The implications of inadequate leukocyte reduction (LR) with SCT units on clinical outcomes remain uncertain[8-11]. There is also limited evidence regarding inaccuracies in HbS or hemoglobinopathy testing from these units. Institutions must balance safety with the costs and availability of HbS-negative units. While transfusing HbS-negative units is standard practice, some institutions are reevaluating this approach due to screening costs and donor deferrals. The Association for the Advancement of Blood & Biotherapies (AABB) guidelines permit transfusion services to tailor their policies based on specific needs and risk assessments.

V. Age of the RBC Unit

Question: Does the age of the RBC unit matter?

Current evidence suggests the age of RBCs does not significantly affect neonatal outcomes outside of potassium load concerns. The Age of Red Blood Cells in Premature Infants (ARIPI) study randomly assigned low-birthweight neonates to receive RBCs that were less than or equal to seven days old (mean=5.1 days) or standard-issue RBCs divided into aliquots and stored for 2 to 42 days (mean =14.6)[12]. The study found no differences in primary endpoints (necrotizing enterocolitis, intraventricular hemorrhage, and bronchopulmonary dysplasia) between neonates in the two arms. For LV transfusions (>20 mL/kg), using RBCs less than 14 days old is recommended, though practices vary between 3-21 days.

VI. Potassium Load Concern and Mitigation Strategies

Question: What are the specific strategies to mitigate potassium load concerns during high-volume transfusions in neonates?

When a LV transfusion (> 20 mL/kg) is needed due to the neonate's weight and anemia severity, the primary concern when issuing this unit is the potential high potassium load in the extracellular fluid during RBC storage. A retrospective review reported that transfusion associated hyperkalemia (TAH) occurred in 0.93 percent of transfused pediatric patients, with a higher infusion rate associated with greater risk[13]. To mitigate the risk of TAH in patients receiving LV transfusions, particularly in

neonates with elevated plasma potassium levels or impaired renal function, the following recommendations include:

- Limit the transfusion rate to **a maximum of 0.5 mL/kg/minute, not to exceed a rate of 5 mL/min for infants <10 kg**[14];
- Use fresher units (collected within 7 days) and irradiated just before use;
- Transfuse irradiated units within **12-24 hours of irradiation**;
- Wash or reduce supernatant in units if freshly irradiated blood is unavailable, balancing this approach with the risk of hemolysis and mechanical damage to the RBCs as well as potassium reaccumulation[15,16]. Use a combination of blood products and crystalloids to **dilute potassium concentration**; and
- Have insulin and glucose available to manage potassium overload.

To ensure optimal neonatal transfusion practices, decisions regarding neonatal RBC preparations should be made by the medical director of the transfusion service in consultation with institutional neonatologists, taking into account both established guidelines and the individual needs of each neonate. Clear policies regarding RBC preparations should be established. These policies should be regularly audited and updated based on the latest evidence and institutional outcomes, promoting a culture of continuous improvement in neonatal transfusion medicine. ■

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