Whole Blood vs. Component Prime Therapy in Neonatal & Pediatric CPB

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Disclosure
Nothing to disclose

Objectives

• Review prime and patient management challenges for neonatal CPB
• Discuss outcomes associated with FWB vs. RBC/FFP component priming strategies
• Preliminary data from the 2017 Groom International Pediatric Perfusion Survey
• Discuss optimal priming strategies and interventions to reduce CPB-related morbidities

Historical Perspective

Cardiopulmonary Bypass Principles and Practice: Gravlee, Stammers, Ungerleider

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<td>Pragmatic Primer Function</td>
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• Perfusion started out with primes of:
  - Normal composition (whole blood)
  - Normal flows (70-80 mL/kg/min)
  - Normal blood pressures

• Hypothermia was used to protect organs from "adverse effects" of:
  - Low flow
  - Hemodilution

• Around 1960 surgeons began using crystalloid solutions or plasma-expanding colloids to reduce or eliminate blood from prime
Neonatal Challenges

- M&M during neonatal heart surgery has dramatically improved over the past decade; however it remains higher than in older children and adults.
- Neonates endure the equivalent of a complete exchange transfusion or more despite attempts to miniaturize ECC’s.
- Increased bleeding and allogeneic transfusion requirements vary inversely with the age and size of infants requiring cardiac surgery.
- Exaggerated dilutional disruptions of coagulation.

- Coagulation disturbances leading to postop bleeding in neonates are multifactorial:
  - 52% of neonates undergoing CPB had factor levels significantly less than normal, due to immature hepatic system that continues to mature throughout first 2-3 weeks of life.
  - Hemodilution: Clinically significant thrombocytopenia (>50% decrease from baseline).
  - Systemic Inflammation.
  - Prolonged bypass times.
  - Use of DHCA.
- These insults contribute to:
  - Capillary leak syndrome.
  - Generalized edema.
  - Myocardial injury.
  - Multisystem organ failure.

Balanced Physiologic Prime

- The prime is the largest volume of fluid administered to the patient during surgery, and is given instantaneously, unlike other perioperative fluids.
- The prime can be a significant determinant in the patient’s metabolic response to the cardiac operation due to:
  - Prime composition.
  - Disparities in size between the prime and patient CBV.
  - Deleterious effects of CPB being more pronounced due to immature tissue and organ function.

Whole Blood vs. PRBC Rationale

- FWB Proponents:
  - Lessen severity of coagulopathy and inflammation.
  - Reduce overall donor exposure.
  - Improved postop hemostasis.
- Disadvantages of using FWB:
  - Difficulties with procurement.
  - Expedited testing required.
  - Loss of component inventory in blood bank.
Whole Blood vs. PRBC Transfusion

- Studies document the detrimental effects of stored RBC's contributing to severe complications:
  - High levels of activated inflammatory cells
  - Acidosis
  - Hypoproteinemia
  - Electrolyte imbalances

- Although PRBC's are the most non-physiologic, FWB is not without derangements:

Single-center, randomized, double-blind, controlled trial

Prime component description:
- FWB: 1/2 in prime, 1/2 during rewarming (≤ 48 hrs stored at 2-6°C) n=96; median age = 47.6 hrs
- Reconstituted blood (50% PRBC stored at 1-6°C & 50% FFP) n=104; median age = 139.5 hrs (<5 days)

- 200 infants < 1 year were included:
  - Clinical outcomes and serologic measures of SIRS and myocardial injury were compared
  - Only patients utilizing a blood prime and a specific surgical team were eligible

- Strict clinical guidelines for postop transfusion were instituted to allow comparison of blood-transfusion requirements between groups.

Intraop & Postop Outcomes

- No significant differences between groups in:
  - Intraoperative variables
  - Transfusion requirements
  - Rate of death from all causes
  - Frequency of severe postoperative clinical course
  - Delayed sternal closure
  - Need for EOIIOO support
  - Overall number of postoperative complications

Primary Outcome Variables

- No significant differences between primary outcome variables
- The reconstituted blood group trended (P=0.10) toward a lower median score than the fresh WB group

NOTE: For the subgroup analysis to include days spent in ICU to postop day 28, including examination of cohorts with single-ventricle lesions, cohorts with two-ventricle lesions, and cohorts grouped according to age (≤ 28 days, > 28 days), the results revealed no significant differences in outcomes between patients who received fresh WB and those who received reconstituted blood.
Differences in other clinical variables proved to be significant:

- ICU LOS significantly shorter for PRBC
- Cumulative fluid balance significantly smaller at 48 hours and trend toward less edema throughout the 72-hour period

Clinical Variables: ICU Length of Stay, Cumulative Fluid Balance

Clinical Outcomes

- Mechanical ventilation in PRBC group trended toward shorter duration

The following parameters were similar in both groups:
- Early postop chest tube output
- Blood product transfusion requirements
- Levels of serum mediators of inflammation
- Cardiac Troponin I
- Perioperative inotropic support
- Myocardial injury
- SIRS

Donor exposure in reconstituted-blood group was greater than the FWB group (4.0 donors vs. 3.5 donors, P = 0.05)

Due to obligate use of two donors for blood reconstitution, as opposed to a single donor for FWB

Clinical Variables: Duration of Mechanical Ventilation

Clinical Outcomes

- Additional charge of $110 for FWB
- Extended stay in ICU associated with FWB = $5,750.00 and doesn’t include charges for medications and other therapies associated with prolonged intensive care
- Approximately 20,000 CHD operations performed annually in US, the cost savings could be substantial

COST

- The use of FWB for CPB priming has no advantage over the use of a combination of PRBC and FFP during CHD surgery
- Moreover, circuit priming with FWB is associated with:
  - increased LOS in the ICU (70.5 hrs vs. 97.0 hrs, P=0.04)
  - increased perioperative fluid overload (6.9 mL/kg vs. 28.8 mL/kg, P=0.003)
- FWB trended toward an increased duration of mechanical ventilation (P=0.09)

CONCLUSION
• Retrospective evaluation 100 patients to analyze if there were benefits to their FWB and Pre-RUF primes on outcomes in neonatal & pediatric cardiac surgery
  
  - 3 groups all Pre-RUF:
    - FWB vs. PRBC prime
    - < 5 kg FWB vs. < 5 kg PRBC prime
    - 5+ kg FWB vs. 5+ kg PRBC prime

  JECT 2007; 39:168-176
  Children's Hospital Illinois

• Results:
  - Perioperative inotrope and post op blood loss did not differ among groups
  - No statistical differences between following outcomes:
    - Intra-op death
    - Intra-op intubation
    - Delayed sternal closure
    - Mediastinal reexploration

• Prospective observational study
  - Authors hypothesized in neonates and infants, a small volume CPB prime consisting of either reconstituted WB (RWB) or non-fresh WB (NF-WB) stored for < 7 days would:
    - Result in significant thrombocytopenia with
    - Relative preservation of coagulation factor levels

• RESULTS:
  - Hemostatic composition of the prime was the same following the use of either NF-WB or RWB
Dilutional Effect

- Both NF-WB and RWB prime for neonates/infants to reach a post-dilutional Hct of 30%:
  - Induces clinically significant dilutional thrombocytopenia
  - With less significant reductions in fibrinogen, FX, FV, FVIII, FXI, FXII, plasminogen, and AT-III
- Platelet count decreased by 70-80% from baseline to end of CPB:
  - ~60% of the decrease was dilutional
- Dilutional thrombocytopenia and hypofibrinogenemia also observed in other pediatric studies with large prime volumes of either PRBC or NF-WB were used to reach a target Hct

International Pediatric Perfusion Practice Surveys

- 2002 Survey: No mention of WB primes
- 2005 Survey: 24% of centers use WB for priming neonatal circuits
- 2011 Survey: No mention of WB priming

2017 Groom International Pediatric Survey

- NORTH AMERICA:
  - 19,314 pediatric/infant/neonatal procedures @ 92 centers (89 US / 3 Canada) in North America over a 3-year period (6,438 procedures/year)
- NON-NORTH AMERICA:
  - 26,927 pediatric/infant/neonatal procedures at 67 non-North American centers over a 3-year period (8,975 procedures/year)
**Crystalloid Component of Prime**

2017 Groom International Pediatric Survey Preliminary Results

- Neonatal circuit static prime volume
  - **Average:** 283 mL
  - **Minimum:** 120 mL
  - **Maximum:** 550 mL

**Blood Prime Components**

2017 Groom International Pediatric Survey Preliminary Results

Which of the following blood products do you use to prime the bypass circuit for the following age groups? (select all that apply):

**FWB Conclusions...**

- Techniques and equipment for neonatal CPB have significantly improved over the past 20 years, however optimal priming composition and fluid management for this group of patients remains unclear and varies tremendously from institution to institution.
- Use of FWB in prime has no advantage over RBB for congenital heart surgery and is associated with significantly increased ICU LOS & periop fluid overload.
- Only reproducible advantage to FWB prime is significantly decreased donor exposures:
  - Alleviated by using single donor for PRBC & FFP
  - Other authors have concluded there are no additional benefits for using FWB than decreasing donor exposures.
  - Unable to corroborate positive effects of FWB on postop blood loss or coagulation.
  - Transfusion medicine standards do not support widespread use of FWB.
  - Whole blood is not even available for use at some institutions.

**Availability of Fresh Whole Blood**

- WB transfusion is more common outside the US, especially in developing countries.
- 90% of Vanderbilt University homologous blood products are provided by the local ARC:
  - Nashville ARC will not routinely provide whole blood for transfusion
  - Whole blood requires a physician order and is done as a special collection
  - Utilizing WB would be more difficult from a blood banking perspective as it would limit the availability of specific component transfusions, which is perceived as an advantage over WB transfusions.

- Age of homologous PRBCs:
  - VCH definition of fresh <= 14 days old
  - Pediatric cardiac surgery is usually ~ 2 days old (or generally between 5-14 days)
  - After 14 days, it is used in the adult hospital.
OPTIMIZING NEONATAL PERFUSION

Hemostasis & Factor Replacement:
- Prime volume is a significant predictor of transfusion (P<.001). It is a risk factor we can easily influence.
- Largest contributor to neonatal postop bleeding is dilutional effect of bypass:
  - 70-80% decrease from baseline resulting in clinically significant thrombocytopenia
  - ATIII decrease by 50%

Platelets:
- Thrombocytopenia prior to termination of CPB or following protamine administration correlates with excessive postop blood loss in children.
- Volume-reduced platelets are effective in treating thrombocytopenia in a linear dose-related manner.

Fibrinogen:
- Hypofibrinogenemia is a key factor in dilutional coagulopathy following cardiac surgery.
- Neonatal and infant hemostasis may be further compromised by dysfunctional fibrinogen.
- Traditional thresholds for fibrinogen replacement following CPB are ~100-150 mg/dl.
- Aggressive replacement of fibrinogen before concentrations fall below 100 mg/dl has been shown to reduce transfusion requirements despite the presence of thrombocytopenia.

Optimizing Neonatal Perfusion

Fresh blood products:
- Transfusing old blood is an independent predictor of multi-organ failure and in-hospital mortality.
- Increased storage of PRBC's has been associated with an increased risk of postop pneumonia and LOS in cardiac surgical population.

Pre-bypass Ultrafiltration (PreBUF):
- Reduces inflammatory, electrolyte, and metabolic disturbances and prevents large osmolar fluxes before initiating CPB.
- Balanced ultrafiltered prime may be particularly advantageous in single ventricle patients with:
  - higher markers of inflammation
  - anemia/postop morbidity
- An easy & effective way to provide a balanced, physiological prime whether FWB or RWB is used.

Multidisciplinary Communication:
- Coordinate post-bypass factor administration by anesthesia with our ability to decrease pt CBV and increase Hct during MUF.

Utilizing priming protocols of combining various electrolyte solutions to match the patients physiology as closely as possible (TCH):
- Develop strategies to quantify/optimize COP in the prime and during bypass:
  - Lower COP's are associated with longer ICU stay and higher mortality.
- Need to continue looking for existing as well as emerging strategies and techniques to reduce CPB-related morbidities and optimize the neonates response to CPB.
Previous studies using fresh WB to either prime the pump or meet postop transfusion needs have reported conflicting results.

Objective: Compared effects of reconstituted fresh WB (RFWB) against standard blood component therapy (PRBC’s) used in the prime, throughout CPB and for all transfusion requirements within the first 24 hours postoperatively in neonates undergoing CPB.

Methods:
- Patients < 1 month of age randomized to receive either RFWB (n=31) or PRBC therapy (n=33).
- Primary Outcome: chest tube drainage.
- Secondary Outcome: transfusion needs, inotrope score, ventilation time, and hospital length of stay.

Blood Product Preparation:
- Canadian Blood Services (CBS) require all donor blood be separated into components immediately after collection and leukocyte reduced by filtration before storage:
  - Red blood cells
  - Random donor platelets
  - FFP
- All donor blood collected into bags containing citrate phosphate double dextrose (CPDD):
  - PRBC components were stored in AS-3 preservative and stored at 33.8°F to 42.8°F.
  - All plasma was frozen within 8 hours of donation and stored at -0.4°F.
  - Platelets were continually agitated during storage at 68°F to 75.2°F.
- On the DOS morning, one of the RFWB units was prepared by reconstituting the components from the single donor previously described:
  - All RFWB units were collected 2 days before the morning of operation.
  - PRBC and platelets were irradiated on the morning of the operation before either reconstitution or release as individual components.
  - Platelets were random single donor platelets collected 2–5 days (median 4 days) before DOS.

Reconstituted FWB vs. Reconstituted

Table A. Medical records of RFWB group versus component therapy

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<td>Blood donor unit exposure (days)</td>
<td>7.5 [4-11]</td>
<td>7.5 [4-11]</td>
<td>7.5 [4-11]</td>
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<td>Blood cell significantly older at prime (days)</td>
<td>30.8 [17.8-53.8]</td>
<td>30.8 [17.8-53.8]</td>
<td>30.8 [17.8-53.8]</td>
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<td>Bleeding described by surgeon more frequently as moderate or severe (days)</td>
<td>44.8 [29.8-69.8]</td>
<td>44.8 [29.8-69.8]</td>
<td>44.8 [29.8-69.8]</td>
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<td>Median total ventilation hours or time to first extubation</td>
<td>119; 28-480</td>
<td>164; 14-192</td>
<td>164; 14-192</td>
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No difference between groups:
- In median total volume transfused within study period.
The use of RFWB affects 3 important parameters of blood transfusion:

- Age of infused cells
- Number of allogeneic donor exposures
- Platelet count during bypass

Because the effect of RFWB is likely multifactorial, further analyses quantified the effect of each component:

- Chest tube loss at 24 hours, inotropic score at 24 hours, duration of ventilation, and hospital stay were all found to be significantly associated with age of blood product, exposure to allogeneic donors, and higher platelet count at end of bypass

Component group:

- Lower platelet count at end of bypass and exposure to higher number of allogeneic donors were independent predictors of higher inotropic score at 24 hours
- Lower platelet count at end of bypass and older age of blood cells were independent predictors of longer duration of hospital stay

Discussion:

- RFWB may be superior to traditional WB owing to:
  - Pre-storage leukocyte depletion: standard for blood component preparation in Canada; reducing leukocytes to \(10^4\); a value below which alloimmunization or suppression does not occur
  - Storage of platelets at room temperature: exhibit better hemostatic properties than when stored at cold temperatures, the routine in traditional WB storage

- Difference in age of blood between the two study groups (1.9 ± 0.3 vs. 13.6 ± 7.7 days) contributed to the improved clinical outcomes in the RFWB group:
  - Significantly lower median inotropic score at 24 hours than component group

- Median age of PRBC's was 14 days:
  - Increased storage of PRBC's has been associated with an increase in risk of postop pneumonia and an increased length of stay in cardiac surgical population
  - Inflammatory markers showed a significantly greater increase in the component group (IL-8)

Conclusion:

- Advocates the use of single donor RFWB to prime the bypass circuit, throughout CPB, and for transfusion requirements during the first 24 hours postop
- Neonates who received RFWB had significantly improved clinical outcomes, including:
  - Less postop chest tube volume loss during first 24 hours
  - Significant lower median inotropic scores
  - Decreased ventilation time
  - Reduced hospital length of stay

- Three factors in the RFWB group that independently contributed to these improved outcomes:
  - Higher platelet count at 10 minutes and end of bypass
  - Reduced number of allogeneic donor exposures
  - Younger age of blood products

Gruenwald study contradicts results from Mou and colleagues previous randomized controlled trial, which found no differences in postop outcomes between component vs. FWB:

- Additionally, Mou study showed some secondary clinical measures and advantage for component therapy

- Use of FFP for priming only while using component therapy for further transfusion requirements may have obscured the effect of FWB

- The use of blood in both arms of the study that had not been leukodepleted could offset gains made by using FWB

While Gruenwald showed clinical advantages of using RFWB in neonatal cardiac surgery, logistical issues may prevent replicating this strategy (single donor, fractionating/recombining components, maintaining platelets at room temperature while being agitated until recombination)

- Age of RBC's and platelets in component group was older than that used in other centers, but was within acceptable CBS standard operating procedures

- Assessment of blood loss in postop period only took into account drainage from chest tubes and did not account for blood collecting in pleural cavity or mediastinum for patients with open chests postop

- Could underestimate total blood loss since difference was unevenly distributed between experimental groups