Blood transfusion management

BAPA refresher course

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Anesthesiology Unit
Conflicts of interest:

Speaker’s fees Medtronic
Consensus Recommendations for RBC Transfusion Practice in Critically Ill Children From the Pediatric Critical Care Transfusion and Anemia Expertise Initiative

Valentine, Stacey L.; Bembea, Melania M.; Muszynski, Jennifer A.; Cholette, Jill M.; Doctor, Allan; Spinella, Phillip C.; Steiner, Marie E.; Tucci, Marisa; Hassan, Nabil E.; Parker, Robert I.; Lacroix, Jacques; Argent, Andrew; Carson, Jeffrey L.; Remy, Kenneth E.; Demaret, Pierre; Emeriaud, Guillaume; Kneyber, Martin C. J.; Guzzetta, Nina; Hall, Mark W.; Macrae, Duncan; Karam, Oliver; Russell, Robert T.; Stricker, Paul A.; Vogel, Adam M.; Tasker, Robert C.; Turgeon, Alexis F.; Schwartz, Steven M.; Willems, Ariane; Josephson, Cassandra D.; Luban, Naomi L. C.; Lehmann, Leslie E.; Stanworth, Simon J.; Zantek, Nicole D.; Bunchman, Timothy E.; Cheifetz, Ira M.; Fortenberry, James D.; Delaney, Meghan; van de Watering, Leo; Robinson, Karen A.; Malone, Sara; Steffen, Katherine M.; Bateman, Scot T.; for the Pediatric Critical Care Transfusion and Anemia Expertise Initiative (TAXI), in collaboration with the Pediatric Critical Care Blood Research N

Abstract:

Objectives:
To date, there are no published guidelines to direct RBC transfusion decision-making specifically for critically ill children. We present the recommendations from the Pediatric Critical Care Transfusion and Anemia Expertise Initiative.

Design:
Consensus conference series of multidisciplinary, international experts in RBC transfusion management of critically ill children.

Setting:
Not applicable.

Intervention:
None.

Subjects:
Children with, or children at risk for, critical illness who receive or are at risk for receiving a RBC transfusion.

Methods:
A panel of 38 content and four methodology experts met over the course of 2 years to develop evidence-based, and when evidence lacking, expert consensus-based recommendations regarding decision-making for RBC transfusion management and research priorities for transfusion in critically ill children. The experts focused on nine specific populations of critically ill children: general, respiratory failure, nonhemorrhagic shock, nonlife-threatening bleeding or hemorrhagic shock, acute brain injury, acquired/congenital heart disease, sickle cell/oncology/transplant, extracorporeal membrane oxygenation/ventricular assist/ renal replacement support, and alternative processing. Data to formulate evidence-based and expert consensus recommendations were selected based on searches of PubMed, EMBASE, and Cochrane Library from 1980 to May 2017. Agreement was obtained using the Research and Development/UCLA Appropriateness Method. Results were summarized using the Grading of Recommendations Assessment, Development, and Evaluation method.

Measurements and Results:
The Transfusion and Anemia Expertise Initiative consensus conference developed and reached consensus on a total of 102 recommendations (57 clinical [20 evidence based, 37 expert consensus], 45 research recommendations). All final recommendations met agreement, defined a priori as greater than 80%. A decision tree to aid clinicians was created based on the clinical recommendations.

Conclusions:
The Transfusion and Anemia Expertise Initiative recommendations provide important clinical guidance and applicable tools to avoid unnecessary RBC transfusions. Research recommendations identify areas of focus for future investigation to improve outcomes and safety for RBC transfusion.
Oncologic Disease

Recommendation

R7.5 In children with oncologic disease who are critically ill or at risk of critical illness, we recommend undertaking well-designed registries or expanding current initiatives to inform future research investigating the risks, benefits and alternatives of transfusion practice. Consensus panel expertise. Voting data (n = 29): 97% agreement, median 9, IQR 8–9.

8.2 In critically ill children on ECMO, we recommend measuring Hb concentration before all RBC transfusion, unless the patient experiences life-threatening bleeding. Consensus panel expertise, 97% Agreement, n = 35, median 8 (IQR 8–9)
**Children With Nonhemorrhagic Shock**

**Recommendations**

3.1 In critically ill children with non-hemorrhagic shock, we recommend considering all possible strategies to augment oxygen delivery and decrease oxygen demand, instead of only considering RBC transfusion. *Consensus panel expertise, 97% Agreement, Median 9 IQR 8–9*

3.2 We cannot recommend a specific RBC transfusion decision making strategy using physiologic based metrics and biomarkers in critically ill children with non-hemorrhagic shock. *Consensus panel expertise, 97% Agreement, Median 8, IQR 8–9*

6.1 In children with cardiac disease we recommend optimization of all the components contributing to oxygen delivery, including but not limited to achievement/maintenance of: normal sinus rhythm and/or heart rate control, optimal preload and contractility, optimal right ventricular and left ventricular afterload, adequate oxygenation and/or reduction of oxygen demand, as appropriate before initiation of RBC transfusion, except in the case of hemorrhagic shock. *Consensus panel expertise; 94% Agreement (n = 35), Median 8, IQR 8–9*
Questions are guaranteed in life; Answers aren't.
Paediatric Anaesthesia Quality Checklist

The 10 - N - Paediatric Anaesthesia Quality Checklist

1. No Fear
2. Normovolaemia
3. Normotension
4. Normocardia
5. Normoxaemia
6. Normocapnia
7. Normonatraemia
8. Normoglycaemia
9. Normothermia
10. No Pain

⇒ 5 of the 10-N´s can be influenced by adequate blood management
Patient Blood Management programs

• Well recognized & appreciated in adults
• Result of evidence - based medicine in adults
• Neonates & children: physiological differences
  
  : higher average Hb concentrations
  
  : higher $O_2$ consumptions compared to adults
Patient Blood Management programs

- Blood utilization review & auditing: compared with current pediatric evidence based transfusion guidelines
- Perioperative anemia management
- Standard procedures for massive transfusion
- Maintaining a hemovigilance program
- Appropriate blood product selection
  (irradiated, leukoreduces, washed,..)
<table>
<thead>
<tr>
<th>Preoperative strategies to augment hemoglobin levels</th>
<th>Intraoperative blood management strategies</th>
<th>Postoperative blood management strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Restrictive transfusion</strong> threshold strategies</td>
<td>** Restrictive transfusion** threshold strategies</td>
<td><strong>Restrictive transfusion</strong> threshold strategies</td>
</tr>
<tr>
<td>Minimize blood draws preoperatively</td>
<td>Minimize blood draws intraoperatively</td>
<td>Minimize blood draws postoperatively</td>
</tr>
<tr>
<td>Oral and intravenous iron replacement (with or without concomitant folate)</td>
<td>Intraoperative blood recovery and cell salvage</td>
<td>Postoperative blood recovery</td>
</tr>
<tr>
<td>Erythropoiesis-stimulating agents, eg, erythropoietin (with or without concomitant iron and folate)</td>
<td>Acute normovolemic hemodilution</td>
<td>Repleting vitamin K postoperatively</td>
</tr>
<tr>
<td></td>
<td>Prophylactic use of fibrinogen concentrates</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Use of antifibrinolytic agents: TXA, EACA</td>
<td></td>
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<tr>
<td></td>
<td>Use of point-of-care testing (eg, TEG, TEG) to guide transfusion decisions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FWB or reconstituted whole blood</td>
<td></td>
</tr>
</tbody>
</table>

* Please note that these are potentially applicable strategies and, currently, data are lacking/limited for many of these approaches in the pediatric age group.
Transfusion medicine community: 5 rights

1. Transfusing the right product
2. Transfusing in the right dose
3. Transfusing to the right patient
4. Transfusing at the right time
5. Transfusing for the right reason
Patient Blood Management programs

Blood transfusions in children: a multi-institutional analysis of practices and complications

Anthony D. Slonim, Jill G. Joseph, Wendy M. Turenne, Aditi Sharangpani, and Naomi L.C. Luban

10,7 complications VS 2,5 complications
Per 1000 products transfused
Transfusing the right product & for the right reason

- Packed RBC
- FFP
- Platelet concentrate
- Fibrinogen (cryoprecipitate)
- Others: PPC, F VIIa
Packed RBC

**Definition of anemia??**

- **Children:** ≤ 7 g/dL
  - ≤ 5 g/dL......Pediatric Critical Care Transfusion & Anemia Expertise
- **In neonates:** ≤ 8 g/dL (RCT of restrictive vs liberal transfusion)
- **Preterm infants**

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**Table 4. Red blood cell transfusion thresholds for preterm infants**

<table>
<thead>
<tr>
<th>Age</th>
<th>BSH Ventilated</th>
<th>BSH NIPPV</th>
<th>BSH No support</th>
<th>NBA, Australia Preterm &lt;37 weeks</th>
<th>Canada Infants with anaemia of prematurity</th>
</tr>
</thead>
<tbody>
<tr>
<td>First 24 h (g L⁻¹)</td>
<td>&lt;120 &lt;100</td>
<td>&lt;100</td>
<td></td>
<td>Not specifically stated, assumed to be Week 1</td>
<td>Not specifically stated, assumed to be Week 1</td>
</tr>
<tr>
<td>Week 1 (g L⁻¹)</td>
<td>&lt;120 &lt;100</td>
<td>&lt;100</td>
<td></td>
<td>110–130 100–120</td>
<td>&lt;115 &lt;110</td>
</tr>
<tr>
<td>Week 2 (g L⁻¹)</td>
<td>&lt;100 &lt;95</td>
<td>&lt;75</td>
<td></td>
<td>100–125 85–100</td>
<td>&lt;100 &lt;85</td>
</tr>
<tr>
<td>Week 3 (g L⁻¹)</td>
<td>&lt;100 &lt;85</td>
<td>&lt;75</td>
<td></td>
<td>85–110 70–100</td>
<td>&lt;85 &lt;75</td>
</tr>
</tbody>
</table>

BSH, British Society for Haematology; CPAP, continuous positive airway pressure; FiO₂, fraction of inspired oxygen; NBA, National Blood Authority; NIPPV, nasal-intermittent positive pressure ventilation; PPV, positive pressure ventilation.
Risks of Anemia

Relationship Between Preoperative Anemia and In-Hospital Mortality in Children Undergoing Noncardiac Surgery.
Faraoni D¹, DiNardo JA, Goobie SM.

Abstract

BACKGROUND: The relationship between preoperative anemia and in-hospital mortality has not been investigated in the pediatric surgical population. We hypothesized that children with preoperative anemia undergoing noncardiac surgery may have an increased risk of in-hospital mortality.

METHODS: We identified all children between 1 and 18 years of age with a recorded preoperative hematocrit (HCT) in the 2012, 2013, and 2014 American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) pediatric databases. The endpoint was defined as the incidence of in-hospital mortality. Children with preoperative anemia were identified based on their preoperative HCT. Demographic and surgical characteristics, as well as comorbidities, were considered potential confounding variables in a multivariable logistic regression analysis. A sensitivity analysis was performed using propensity-matched analysis.

RESULTS: Among the 183,833 children included in the 2012, 2013, and 2014 ACS NSQIP database, 74,508 had a preoperative HCT recorded (41%). After exclusion of all children <1 year of age (n = 12,063), those with congenital heart disease (n = 8943), and those who received a preoperative red blood cell (RBC) transfusion (n = 1880), 12,551 (24%) children were anemic, and 39,071 (76%) were nonanemic. The median preoperative HCT was 33% (interquartile range, 31-35) in anemic children, and 39% (interquartile range, 37-42) in nonanemic children (P < .001). Using multivariable logistic regression analysis, and after adjustment for RBC transfusion (OR, 2.13; 95% CI, 1.39-3.26; P < .001), we observed that preoperative anemia was associated with higher odds for in-hospital mortality (OR, 2.17; 95% CI, 1.48-3.19; P < .001). After propensity matching, the presence of anemia was also associated with higher odds of in-hospital mortality (OR, 1.75; 95% CI, 1.15-2.65; P = .004).

CONCLUSIONS: Our study demonstrates that children with preoperative anemia are at increased risk for in-hospital mortality. Further studies are needed to assess whether the correction of preoperative HCT, through the development of a patient blood management program, improves patient outcomes or simply reduces the need for transfusions.
**Figure 2.** Incidence of in-hospital mortality in children with anemia for those with and without red blood cell transfusion. Unadjusted *P* value obtained from the $\chi^2$ test.
Figure 3. Unadjusted and adjusted odds ratio for in-hospital mortality in children with anemia. Odds ratio and 95% confidence interval (CI) obtained from univariable (unadjusted), multivariable logistic regression after adjustment for red blood cell transfusion, neurological disorders, emergency surgery, preoperative inotropic support, mechanical ventilation, neoplasm, and American Society of Anesthesiologists (ASA) physical status classification ≥3 (adjusted) (anemic, n = 12,551; and nonanemic children, n = 39,071), and propensity-matched analysis (anemic, n = 12,160; and nonanemic children, n = 12,160).
Restrictive vs liberal transfusion strategy in children

What is the outcome you are looking at?
Randomized trial of liberal versus restrictive guidelines for red blood cell transfusion in preterm infants.

Bell EF, Strauss RG, Widness JA, Mahoney LT, Mock DM, Seward VJ, Cress GA, Johnson KJ, Kromer IJ, Zimmerman MB.

Abstract

OBJECTIVE: Although many centers have introduced more restrictive transfusion policies for preterm infants in recent years, the benefits and adverse consequences of allowing lower hematocrit levels have not been systematically evaluated. The objective of this study was to determine if restrictive guidelines for red blood cell (RBC) transfusions for preterm infants can reduce the number of transfusions without adverse consequences.

DESIGN, SETTING, AND PATIENTS: We enrolled 100 hospitalized preterm infants with birth weights of 500 to 1300 g into a randomized condition improved reflected the widely held belief that older, more stable infants could safely tolerate lower hematocrit levels. While tracheally intubated for assisted ventilation (phase 1), infants in the liberal- and restrictive-transfusion groups received an RBC transfusion if their hematocrit levels fell to <46% and <34%, respectively. While receiving nasal continuous positive airway pressure or supplemental oxygen (phase 2), their hematocrit levels were kept at >38% and >28%, respectively, and if requiring neither positive pressure nor oxygen (phase 3), they were kept at >30% and >22%, respectively. These threshold levels were developed by diverging above and below the hematocrit levels.

RESULTS: Infants in the liberal-transfusion group received more RBC transfusions (5.2 +/- 4.5 [mean +/- SD] vs 3.3 +/- 2.9 in the restrictive-transfusion group). However, the number of donors to whom the infants were exposed was not significantly different (2.8 +/- 2.5 vs 2.2 +/- 2.0). There was no difference between the groups in the percentage of infants who avoided transfusions altogether (12% in the liberal-transfusion group versus 10% in the restrictive-transfusion group). Infants in the restrictive-transfusion group were more likely to have intraparenchymal brain hemorrhage or periventricular leukomalacia, and they had more frequent episodes of apnea, including both mild and severe episodes.

CONCLUSIONS: Although both transfusion programs were well tolerated, our finding of more frequent major adverse neurologic events in the restrictive RBC-transfusion group suggests that the practice of restrictive transfusions may be harmful to preterm infants.
The Premature Infants in Need of Transfusion (PINT) study: a randomized, controlled trial of a restrictive (low) versus liberal (high) transfusion threshold for extremely low birth weight infants.


Author information

Abstract

OBJECTIVE: To determine whether different transfusion thresholds for extremely low birth weight infants have different rates of primary outcomes.

STUDY DESIGN: Infants weighing <1000 g birth weight were randomly assigned within 48 hours of birth to a transfusion algorithm of either low or high hemoglobin transfusion thresholds. The composite primary outcome was death before home discharge or survival with any of either severe retinopathy, bronchopulmonary dysplasia, or brain injury on cranial ultrasound. Morbidity outcomes were assessed, blinded to allocation.

RESULTS: Four hundred fifty-one infants were randomly assigned to low (n = 223) or high (n = 228) hemoglobin thresholds. Groups were similar, with mean birth weight of 770 g and gestational age of 26 weeks. Fewer infants received one or more transfusions in the low threshold group (89% low versus 95% high, P = .037). Rates of the primary outcome were 74.0% in the low threshold group and 69.7% in the high (P = .25; risk difference, 2.7%; 95% CI -3.7% to 9.2%). There were no statistically significant differences between groups in any secondary outcome.

CONCLUSIONS: In extremely low birth weight infants, maintaining a higher hemoglobin level results in more infants receiving transfusions but confers little evidence of benefit.
Neurodevelopmental outcome of extremely low birth weight infants randomly assigned to restrictive or liberal hemoglobin thresholds for blood transfusion.


Collaborators (33)

Abstract

BACKGROUND AND OBJECTIVE: Extremely low birth weight infants frequently receive red cell transfusions. We sought to determine whether a restrictive versus liberal hemoglobin transfusion threshold results in differences in death or adverse neurodevelopmental outcomes of extremely low birth weight infants.

PATIENTS AND METHODS: Extremely low birth weight infants previously enrolled in the Preterm Infants in Need of Transfusion Trial, a randomized, controlled trial of low versus high hemoglobin transfusion thresholds, were followed up at 18 to 21 months' corrected age. Erythrocyte transfusion was determined by an algorithm of low (restrictive) or high (liberal) hemoglobin transfusion thresholds, differing by 10 to 20 g/L and maintained until first hospital discharge. The primary composite outcome was death or the presence of cerebral palsy, cognitive delay, or severe visual or hearing impairment.

RESULTS: Of 451 enrolled infants, the primary outcome was available in 430. There was no statistically significant difference in the primary outcome, found in 94 (45%) of 208 in the restrictive group and 82 (38%) of 213 in the liberal group. There were no statistically significant differences in preplanned secondary outcomes. However, the difference in cognitive delay (Mental Development Index score < 70) approached statistical significance. A posthoc analysis with cognitive delay redefined (Mental Development Index score < 85) showed a significant difference favoring the liberal threshold group.

CONCLUSIONS: Maintaining the hemoglobin of extremely low birth weight infants at these restrictive rather than liberal transfusion thresholds did not result in a statistically significant difference in combined death or severe adverse neurodevelopmental outcome.

No difference in mortality

No difference in NEC

No difference in CLD

No difference in ROP

No difference in IVH
Neurodevelopmental outcome

*Ongoing phase III transfusion studies:*

1. ETTNO trial: Effects of Transfusion Threshold on Neurocognitive Outcome of Extremely low Birth Weight Infants
2. TOP trial: Transfusion of prematures

Whether higher Hb values lead to:
- Improvement in survival (= primary outcome)
- Rates of neurodevelopmental impairment at 22-26 months of age
Protecting the infant brain during cardiac surgery: a systematic review.

Hirsch JC¹, Jacobs ML, Andropoulos D, Austin EH, Jacobs JP, Licht DJ, Pigula F, Tweddell JS, Gaynor JW.

- Systematic review from 1990 – 2010 of neuromonitoring & neuroprotection strategies
- Infants < 1 year
- 162 manuscripts
- Primary outcome: evidence of structural brain injury in 43%
- Most frequent level of evidence: Class IIb or Level B (42%)
- The only practice with Class IIa or Level A: avoidance of extreme hemodilution
- Conclusion: level of evidence is insufficient to support effectiveness of current neuromonitoring & neuroprotective techniques
How to detect cerebral /organ hypoperfusion?

- Surrogate marker of O₂ delivery/ O₂ consumption
- Combined cerebral/ somatic: useful information
- To date no evidence-based data for its routine use
NIRS-based transfusion of RBC

Abstract

OBJECTIVES: Cerebral non-invasive monitoring of oxygen saturation by near-infrared spectroscopy (rSO2) during paediatric cardiac surgery is supposed to decrease the risk of neurological complications. Since haemoglobin level is one of the factors changing rSO2, we aimed to explore if rSO2 monitoring influences intra-operative RBC (red blood cell) transfusion threshold and volumes, as well as the duration of ICU stay.

METHODS: The design was a retrospective analysis involving 91 children less than 2 years of age (including 16 neonates) with a congenital heart disease requiring surgical treatment with or without cardiopulmonary bypass from January 2006 to August 2009. Systematic rSO2 monitoring was introduced after September 2007 (n=56). The independent factors associated with the intra-operative transfusion threshold haemoglobin (Hb) level>9.5g/dL, total volume of intra-operative RBC transfusion<30mL/kg and ICU stay<6 days were identified by multivariate analysis logistic regression. Data were expressed as medians (25-75%).

RESULTS: Cardiac malformations and demographic characteristics were similar in both periods. Two independent factors, weight and rSO2 monitoring, were identified as independent factors associated with the three end-points. The transfusion threshold, total transfusion volume and ICU stay with and without rSO2 were 9.8 (8.9 to 10.3) versus 8.7 (8.2 to 9.6) g/dL (P<0.0001), 20 (14-49) versus 36 (22.5-51.5) mL/kg (P=0.0165) and 5 (3-8) versus 7 (5-10.7) days (P=0.0084), respectively.

CONCLUSION: rSO2 monitoring changed our transfusion strategy with an earlier transfusion but a reduced total RBC volume and decreased the length of ICU stay.
NIRS-based transfusion of RBC


Red Blood Cell Transfusion Guided by Near Infrared Spectroscopy in Neurocritically Ill Patients with Moderate or Severe Anemia: A Randomized, Controlled Trial.

Leal-Noval SR¹, Arellano-Orden V¹, Muñoz-Gómez M², Cayuela A³, Marín-Caballo A¹, Rincón-Ferrari MD¹, García-Alfaro C¹, Amaya-Villar R¹, Casado-Méndez M¹, Dusseck R¹, Murillo-Cabezas F¹.

Abstract
In neurocritically ill patients (NCPs), the use of hemoglobin level as the sole indicator for red blood cell transfusion (RBCT) can result in under- or over-transfusion. This randomized controlled trial was conducted to ascertain whether a transcranial oxygen saturation (rSO2) threshold, as measured by near-infrared spectroscopy, reduces RBCT requirements in anemic NCPs (closed traumatic brain injury, subarachnoid, or intracerebral hemorrhage), compared with a hemoglobin threshold alone. Patients with hemoglobin 70-100 g/L received RBCTs to attain an rSO2 > 60% (rSO2 arm) or to maintain hemoglobin between 85 and 100 g/L (hemoglobin arm). A total of 102 NCPs (51 in each group) were included in the intention-to-treat analysis, and 97 were included in the per-protocol analysis (51 and 46, respectively). Compared with those from the hemoglobin arm, patients in rSO2 arm received fewer RBC units (1.0 ± 0.1 vs. 1.5 ± 1.4 units/patient; p<0.05) and showed lower hemoglobin levels while in protocol. There were no differences between the study arms regarding the percentage of transfused patients (59% vs. 71%; relative risk 0.83 [95% CI 0.62-1.11]), stay on neurocritical care unit (21 vs. 20 days), unfavorable Glasgow Outcome Scale scores on hospital discharge (57% vs. 71%), in-hospital mortality (6% vs. 10%), or 1 year mortality (24% vs. 24%). Among NCPs with hemoglobin concentrations of 70-85 g/L, withholding transfusion until rSO2 is <60% may result in reduced RBCs requirements compared with routinely transfusing to attain a hemoglobin level >85 g/L. Further studies are required to confirm this finding and its possible impact on clinically significant outcomes.
ASD closure & PAPVR; 4 years; preop Hb = 12.7 g/dL

Hb = 8.1 g/dL: transfusion
When & how much RBC to transfuse?

- **Allowable Blood loss (ABL)**
  
  \[
  ABL = EBV \times \frac{Hct_{\text{starting}} - Hct_{\text{target}}}{Hct_{\text{avg}}}
  \]

- **Transfused volume (PRBC)**
  
  \[
  \text{Transfused volume (PRBC) } = \text{weight (kg) } \times \text{desired Hb increase (g/dL) } \times 5
  \]

- 10 mL/kg PRBC will increase Hb by 2 g/dL
Adverse effects from RBC transfusion

• In general difficult to quantify: ventilated (masking respiratory reactions)
  : draping (no visualisation of urticarial reactions)
  : CPB
  : lack of formal universal definition of reaction

• Transfusion associated circulatory overload
• Transfusion related acute lung injury

Underdiagnosed in neonates with respiratory symptoms
Adverse effects from RBC transfusion

• HyperK & Ventricular fibrillation:

  The « Wake up Safe » initiative from Society of Pediatric Anesthesia recommends that RBC should be fresh (< 1w old) or washed if the patient is < 1y old or weights < 10 kg

• TA - GVHD : very rare with high mortality rate

  : Host (immune incompetence), donor T lymphocyte, and environmental factors (inflammation)

  : irradiated cellular blood components (Japan)

• Allergic reactions : Ig E mediated
How to overcome/treat anemia?

- Autologous blood donation: NO; risks >>>>> benefits
- rhuEPO: very specific cases; guidelines against routine use
- Acute Normovolemic Hemodilution: very specific cases; older children
- Cell salvage except in tumor surgery (dissemination of tumor cells)
- Iron deficiency: exclusive breast feeding is a risk factor
  
  :2–3 mg/kg/d oral iron to preterm /small for gestational age

- Reduce blood draws

! Hb/ Hct: samples from larger veins & arteries = lower than capillary samples
Transfusing the right product & for the right reason

- Packed RBC
- FFP
- Platelet concentrate
- Fibrinogen (cryoprecipitate)
- Others: PPC, F VIIa
FFP

- Decision whether to administer FFP or not: easier
- BUT......
- Evidence guiding transfusion of FFP from all blood products in the neonates is the weakest
- INDICATION: purpura fulminans due to Protein C & Protein S deficiency: congenital thrombotic thrombocytopenic purpura
- Usually 10 – 15 mL/kg when clinical bleeding and standard coagulation tests are 1.5 x nl values:??? Not evidence based
FFP

Standard coagulation tests give inadequate information:

- Reagents used to perform coagulation tests are sensitive to even minor reductions in coagulation factor levels
- Relationship between coagulation factor levels & coagulation test times not linear
- FFP often results in minimal changes in coagulation test results

Point-Of-Care tests: ROTEM / TEG
8.5.2 Coagulation monitoring

Recommendation

We suggest the use of perioperative coagulation analysis using viscoelastic point-of-care monitoring (ROTEM/TEG) for timely detection of coagulation defects including dilutional coagulopathy and hyperfibrinolysis. 2C

Diagnosing paediatric perioperative coagulopathy requires rapid, robust coagulation monitoring, alongside age specific reference ranges.\textsuperscript{1202–1205} ROTEM and TEG can complement standard coagulation tests, especially in the perioperative setting.\textsuperscript{35,114,1136,1206,1207} In a meta-analysis, TEG- or ROTEM-guided transfusion was shown not to affect overall mortality in patients with severe bleeding, but it was associated with significantly reduced bleeding.\textsuperscript{17} Data supporting the effectiveness of ROTEM/TEG-guided paediatric coagulation therapy are limited.\textsuperscript{427,940,1208–1210}
Utilization of frozen plasma, cryoprecipitate, and recombinant factor VIIa for children with hemostatic impairments: An audit of transfusion appropriateness.

Lieberman L.1,2, Lin Y.2,3, Cserti-Gazdewich C1,2, Yi QL.4, Pendergrast J.1,2, Lau W.2,5, Callum J.2,3; From the QUEST-Quality in Utilization Education and Safety in Transfusion-Research Collaborative.1

Abstract

BACKGROUND: Blood transfusions and fractionated products are not without risk and may lead to acute and long-term adverse events. The objective of this study was to evaluate the appropriateness of usage of frozen plasma (FP), cryoprecipitate (CRYO), and recombinant factor VIIa (rVIIa) in a pediatric setting.

METHODS: All orders for FP, CRYO, and rVIIa were prospectively audited over 6 weeks. Data collected included demographics, laboratory values, indication, and adverse reactions. The appropriateness of each order was independently evaluated using adjudication criteria rated by two hematologists.

RESULTS: Two hundred sixty-five products were ordered; 67% of the orders were issued to operating rooms or intensive care units. The most common indication for all products was cardiac surgery. FP was ordered as fluid replacement (15/215; 7%) to correct abnormal coagulation tests (23/215; 11%) and for patients with minor or no bleeding (111/242; 46%). FP was more likely to alter the international normalized ratio (INR) if the INR was over 2.0 (P < 0.0001). The rate of inappropriate products was judged as FP 19%, CRYO 21%, and rVIIa 91%.

CONCLUSION: FP, CRYO, and rVIIa are most commonly used in the operating room and intensive care units. FP was often used for fluid resuscitation and for patients with mild to no bleeding. FP was only effective in lowering the INR when the INR was over 2.0. Use of rVIIa was rarely ordered for an appropriate indication. Results of this study inform its readers where trials of pediatric transfusion should be performed to clarify how these products should be used in clinical practice.
**FIGURE 2** Adjudication of product appropriateness for pediatric plasma (N = 208), cryoprecipitate (n = 45), and recombinant factor VIIa (N = 12)
GUIDELINES BSH

• Against routine use to correct coagulation abnormalities
• Not routinely performing coagulation tests in all neonates
• Indicated: prior to surgery if there is significant coagulopathy
  : acute bleeding secondary to congenital bleeding disorders
  where specific factor replacement is not available (rare!)
  : in the management of active bleeding & significant coagulopathy
  : NOT to be given to « non-bleeding » children with minor coagulopathy even before surgery
Comparison of Fresh Frozen Plasma (FFP) and Plasmalyte® for priming cardiopulmonary bypass in infants and children undergoing open-heart surgery: A double-blinded, randomised study.

Dieu A., Rosal Martins M., Matta A., Khalifa C., Delrez P., Momeni M.
Cliniques universitaires Saint Luc; Université Catholique de Louvain, Dept of Anaesthesiology, Brussels, Belgium

Background and goal of the study
Few studies in infants have investigated whether the addition of FFP to the cardiopulmonary bypass (CPB) priming shows advantages in terms of bleeding and transfusion.\textsuperscript{1,2} We hypothesized that adding FFP to CPB priming is superior when compared with Plasmalyte®.

Material and methods
This prospective double-blinded randomised trial (NCT02567786) included children of all age weighing between 7-15 kg undergoing surgery with CPB. Exclusion criteria were coagulation abnormalities, renal and hepatic dysfunction. Primary endpoint is that adding 15 mL/kg FFP to CPB prime decreases bleeding and/or exposure to blood products up to 6h postoperatively when compared with 15 mL/kg Plasmalyte®. Secondary endpoint is the volume of transfused blood products. RBC was used in the CPB prime to prevent haemodilution and unblinding. The perfusionist was unblinded, Blood was drawn for thromboelastometry (ROTEM®) and platelet aggregometry (Multiplate®) after the induction of anaesthesia, at the end of CPB and at PICU arrival to help in deciding to transfuse in case of bleeding. In total, 60 children will be included. A Student’s t-test, Mann-Whitney or Chi-square tests were used as appropriate.

- No difference between both groups in terms of bleeding or transfusion requirements
- Change in daily practice
Adverse effects of FFP

- Inherent to any allogeneic blood product
- THROMBOTIC COMPLICATIONS
Widespread use of fresh frozen plasma in US children's hospitals despite limited evidence demonstrating a beneficial effect.

Puetz J¹, Witmer C, Huang YS, Raffini L.

Abstract

OBJECTIVES: To determine the pattern, prevalence and potential complications of fresh frozen plasma (FFP) use in US pediatric hospitals from 2002-2009.

STUDY DESIGN: Retrospective cohort study using the Pediatric Health Information System (PHIS) administrative database, which was queried for FFP admissions using diagnostic, procedural, and billing codes. Demographic data, daily use, and procedural codes were used to describe the patient population and pattern of FFP use.

RESULTS: Of 3 252 149 PHIS-recorded admissions, 2.85% had codes consistent with FFP use. This percentage did not change over the course of the study (P=.10). FFP was most commonly administered to children <1 year of age (54%), critically ill children (70%), and those with heart disease (34%). Fifteen percent of FFP-related admissions involved a thrombotic event. The overall mortality rate was 17% and it decreased during the study (P<.001). There was noteworthy variation in the proportion of FFP admissions among participating institutions.

CONCLUSIONS: FFP is commonly used in children admitted to PHIS hospitals. Despite recent expert recommendations highlighting the lack of efficacy in many clinical scenarios, the rate of FFP use does not appear to be changing. Randomized, controlled studies are needed to determine appropriate indications for FFP use and evaluate for potential complications.

Frequent use of fresh frozen plasma is a risk factor for venous thrombosis in extremely low birth weight infants: a matched case-control study.

Maruyama H¹, Kitajima H, Yonemoto N, Fujimura M.

Abstract

Percutaneously inserted central catheters (PICCs) are often used in neonatal medicine. Venous thrombosis (VT) is one of the complications associated with PICC use. According to some reports, fresh frozen plasma (FFP) may be a risk factor for VT. The purpose of this study was to determine whether FFP use is associated with VT in extremely low birth weight infants (ELBWIs). We performed a matched case-control study on risk factors for VT in ELBWIs born over a period of 5 years in the neonatal intensive care unit of a tertiary hospital. Controls were infants from the unit matched for gestational age and birth weight. We performed univariate analyses and created receiver operating characteristic (ROC) curves for the cut-off values of continuous parameters such as FFP. We also conducted multivariate conditional logistic regression analysis and calculated adjusted odds ratios and their 95% confidence intervals. Thirteen VT cases and 34 matched controls were examined. Using an ROC curve, FFP by day 5 > 50 mL/kg was selected as the cut-off value. In multivariate conditional logistic regression analysis, FFP by day 5 > 50 mL/kg exhibited an adjusted odds ratio of 5.88 (95% confidence interval: 1.12-41.81, p = 0.036). FFP by day 5 > 50 mL/kg may be a risk factor for VT in ELBWIs.
Analysis of Patient Characteristics and Risk Factors for Thrombosis After Surgery for Congenital Heart Disease.

Murphy LD¹, Benneyworth BD¹, Moser EAS², Hege KM³, Valentine KM¹, Mastropietro CW¹.

Abstract

OBJECTIVES: Thrombosis is a cause of morbidity in 4-15% of children who undergo pediatric cardiac surgery. Data on how to prevent this complication are sorely needed. We aimed to identify risk factors for thrombosis following pediatric cardiac surgery and determine if use of low molecular weight heparin prophylaxis is associated with a reduction in thrombosis risk.

DESIGN: Retrospective cohort study.

SETTING: Tertiary pediatric cardiovascular ICU.

PATIENTS: Patients who underwent cardiac surgery between June 2014 and December 2015.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Data from patients with venous or arterial thrombosis confirmed by radiologic studies were matched two-to-one to controls based on age, Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery mortality category, and gender. Thrombosis was detected in 33 patients (6.2%): 25 patients (76%) had venous thromboses, five patients (15%) had arterial thromboses, and three patients (9%) had both. Median time to thrombosis detection was 13 days (25-75%; 7-31 d). On multivariate analysis, which included adjustment for postoperative disease severity, fresh frozen plasma exposure was independently associated with thrombosis (odds ratio, 3.7; 95% CI, 1.4-9.4). Twenty-eight patients (85%) had central venous catheter-related thromboses. Low molecular weight heparin prophylaxis use in this subset of patients was not statistically different from controls (50% vs 45%, respectively; p = 0.47). On multivariable analysis, fresh frozen plasma exposure was also independently associated with central venous catheter-related thrombosis (odds ratio, 3.6; 95% CI, 1.2-10.6).

CONCLUSIONS: The occurrence of thrombosis after pediatric cardiac surgery at our institution was 6.2%, similar to what has been reported in other studies, despite frequent use of low molecular weight heparin. Further study is needed to determine the role of low molecular weight heparin for thromboprophylaxis and the relationship between fresh frozen plasma and thrombosis risk in children who undergo cardiac surgery.
Transfusing the right product & for the right reason

- Packed RBC
- FFP
- Platelet concentrate
- Fibrinogen (cryoprecipitate)
- Others: PPC, F VIIa
Platelet concentrate

• Definition: mild = 100 – 150 x 10^9/L
  moderate = 50 – 99 x 10^9/L
  severe = < 50 x 10^9/L

• Definition in neonates less clear:
  Wiedmeier SE et al.
  Predictable increase in platelets 2 x 10^9/L per week increase gestational age

• No clear relationship between thrombocytopenia & clinical bleeding
• No RCT available
• Guidelines British Society of Hematology:
  stable children < 4 m: prophylactic if < 30 x 10^9/L
  stable children > 4 m: prophylactic if < 10 x 10^9/L
Adverse effects platelet concentrate

- Error

- Bacterial & septic infections due to storage at room air

- Allergic reactions

- TACO & TRALI due to the innate plasma component of platelet products
Transfusing the right product & for the right reason

- Packed RBC
- FFP
- Platelet concentrate
- Fibrinogen (cryoprecipitate)
- Others: PPC, F VIIa
Fibrinogen

• Hypofibrinogenemia = major reason for coagulopathic bleeding during complex pediatric surgery (craniosynostosis, cardiac, scoliosis)

• FFP: questionnable efficacy in restoring fibrinogen concentrations

• In adults: in case of thrombocytopenia and/or platelet dysfx, fibrinogen makes a stronger contribution to clot firmness than platelets

Harr et al. Shock 2013; 39:45-9
Fibrinogen

- Best way to analyze fibrinogen concentration and fibrin polymerization: Fibtem
- Fibtem: eliminates the platelet contribution by Cytochalasin D
- In adults: guidelines Eur Society of Anaesthesiology: cutoff Fibtem MCF < 8 mm
Higher fibrinogen concentrations for reduction of transfusion requirements during major paediatric surgery: A prospective randomised controlled trial

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Abstract

Background: Hypofibrinogenenaemia is one of the main reasons for development of perioperative coagulopathy during major paediatric surgery. The aim of this study was to assess whether prophylactic maintenance of higher fibrinogen concentrations through administration of fibrinogen concentrate would decrease the volume of transfused red blood cell (RBCs).

Methods: In this prospective, randomised, clinical trial, patients aged 6 months to 17 yr undergoing craniosynostosis and scoliosis surgery received fibrinogen concentrate (30 mg kg⁻¹) at two predefined intraoperative fibrinogen concentrations [ROTEM® FIBTEM maximum clot firmness (MCF) of <8 mm (conventional) or <13 mm (early substitution)]. Total volume of transfused RBCs was recorded over 24 h after start of surgery.

Results: Thirty children who underwent craniosynostosis surgery and 19 children who underwent scoliosis surgery were treated per protocol. During craniosynostosis surgery, children in the early substitution group received significantly less RBCs (median, 28 ml kg⁻¹; IQR, 21 to 50 ml kg⁻¹) compared with the conventional fibrinogen trigger of <8 mm (median, 56 ml kg⁻¹; IQR, 28 to 62 ml kg⁻¹) (P≤0.03). Calculated blood loss as per cent of estimated total blood volume decreased from a median of 160% (IQR, 110–190%) to a median of 90% (IQR, 78–110%) (P=0.017). No significant changes were observed in the scoliosis surgery population. No bleeding events requiring surgical intervention, postoperative transfusions of RBCs, or treatment-related adverse events were observed.

Conclusions: Intraoperative administration of fibrinogen concentrate using a FIBTEM MCF trigger level of <13 mm can be successfully used to significantly decrease bleeding, and transfusion requirements in the setting of craniosynostosis surgery, but not scoliosis.

Clinical trial registry number: ClinicalTrials.gov NCT01487837.
Economic aspects of intraoperative coagulation management targeting higher fibrinogen concentrations during major craniosynostosis surgery.

Haas T¹, Spielmann N¹, Restin T², Schmidt AR¹, Schmugge M³, Cushing MM⁴.

Author information

Abstract

BACKGROUND: Results of a previously published study demonstrated a significant decrease in transfusion requirements and calculated blood loss for pediatric major craniosynostosis surgery, if a ROTEM® FIBTEM trigger of <13 mm (early substitution group) was applied as compared to a trigger of <8 mm (conventional group). The aim of this study was a posthoc analysis of the costs for this coagulation management.

METHODS: The total volume as well as the number of units or bags for all transfused blood products and coagulation factors were recorded for each case. The number of laboratory and point-of-care coagulation tests was also analyzed. Total blood product costs were calculated according to the local prices per unit.

RESULTS: The total cost for all transfused/administered blood products/coagulation factors per patient was a median of 1023EUR (IQR 850EUR-1058EUR) in the early substitution group as compared to a median of 910EUR (IQR 719EUR-1351EUR) in the conventional group (P = 0.81). No difference in the number of coagulation tests performed was observed.

CONCLUSION: In this study, the use of a higher fibrinogen trigger was not linked to a significant increase in total costs for transfused blood products and coagulation factors, and may offer an economically equivalent approach to coagulation management.

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Fibrinogen

• Dose: Study by Haas 90 (75 – 120) mg/kg

• ! 300 mg/kg: neonate Fibtem values not measurable

• Rule of 10 in bleeding patient: Fibtem A10 < 10 give 50 mg/kg Fibrinogen

• €€€€

• 1L FFP: 2.5 -2.7 g Fibrinogen

• Cryoprecipitate: Not in Europe
  : Different donors
  : VIII + Fibrinogen + Fibronectine + XIII + vWF
  : 2 pools (± 200 mL): 4 g Fibrinogen
Transfusing the right product & for the right reason

- Packed RBC
- FFP
- Platelet concentrate
- Fibrinogen (cryoprecipitate)
- Others: PCC, F VIIa
Prothrombin Complex Concentrate

- Either 3 factors (II, IX, X) or 4 (II, VII, IX, X)
- Clotting factor concentration 25 times higher than normal plasma
- Indication: Vit K antagonists (1 – 2 mL/kg)
  - congenital deficiency of any of these factors when purified specific coagulation factors are not available
- To prevent activation of these factors, most contain heparin
- May also contain natural coagulation inhibitors protein C & S
- Different half – lives of the 4 factors:
  - F II: 60 - 72 h
  - Others: 6 – 24 h
- Adverse effects: HIT – allergic reactions – thromboembolic complications
Factor VIIa

- Very expensive
- Insufficient data in pediatrics
- A prospective, randomized trial in pediatric cardiac surgery failed to prove a significant difference in blood loss when compared to placebo
Antifibrinolytics: Tranexamic acid

• Very effective in major surgery & trauma
• Optimal dosing, timing of administration & pharmacokinetics require studies
• Adverse effects: seizures! At high concentrations

Inhibition of inhibitory glycine and GABA R; these R have lysine binding sites and are mediators of CNS inhibition
• New pharmacokinetic studies

10 – 15 mg/kg over 15 min followed by 5 – 10 mg/Kg/h non-cardiac surgery
Conclusions

• Transfusing & not transfusing = harmful
• More RCT needed to have evidence based data
• Focusing on specific outcomes
• Patient Blood management strategies
Thank you