Virtual Lectures Planning Committee Disclosure Summary

As a provider accredited by ACCME, College of Medicine, Mayo Clinic (Mayo School of CPD) must ensure balance, independence, objectivity and scientific rigor in its educational activities. Course Director(s), Planning Committee Members, Faculty, and all others who are in a position to control the content of this educational activity are required to disclose all relevant financial relationships with any commercial interest related to the subject matter of the educational activity. Safeguards against commercial bias have been put in place. Faculty also will disclose any off label and/or investigational use of pharmaceuticals or instruments discussed in their presentation. Disclosure of these relevant financial relationships will be published in activity materials so those participants in the activity may formulate their own judgments regarding the presentation.

Relevant financial relationship(s) with industry: None

References to off-label and/or investigational usage(s) of pharmaceuticals or instruments in their presentation: None

Listed below are individuals with control of the content of this program who have disclosed:

**Program Speaker**
James Stubbs M.D.

**Program Planning Committee**
Curtis Hanson, M.D.
Bobbi Pritt, M.D., MSc, DTMH
Sharon Preuss
Melissa Peterson
Cold-Stored Whole Blood
&
Cold-Stored Platelets

“Renewed” Thoughts About “Old” Products For Trauma Patients

James R. Stubbs M.D.
Chair, Transfusion Medicine
Mayo Clinic
Rochester, Minnesota
Disclosures

- Nothing to Disclose

Lecture Outline

- Remote Damage Control Resuscitation (RDCR)
  - New “Old” Blood Components that could potentially increase effectiveness of RDCR
  - Low-Titer cold-stored Group O Whole Blood
    - Evidence and rationale for use
    - Mayo implementation
  - Cold-Stored Apheresis Platelets
    - Evidence and rationale for use
    - Mayo implementation
    - Future prospects
  - Transition of both products to RDCR
Damage Control and Remote Damage Control Resuscitation

Damage Control Resuscitation: Directly Addressing the Early Coagulopathy of Trauma

J Trauma 2007; 63:307-310
Trauma Patients

- Early hemostatic control
  - Within first 6 hours of injury
  - Associated with improved outcomes in patients with massive hemorrhage
- Ever growing consensus - Transfusion therapy
  - “The earlier the better”
- DCR – Extended to the pre-hospital setting
  - “Remote” Damage Control Resuscitation (RDCR)

Remote Damage Control Resuscitation

- Why is Remote Damage Control Resuscitation so important?
  - The majority of trauma-related deaths occur before reaching a surgical facility
  - Potentially preventable trauma-related deaths
    - Hemorrhage
      - 80% to 90% of combat-related deaths
      - 66% of civilian deaths
    - Trauma-related deaths occurring with 24 hours of injury
      - Hemorrhage – Cause of death – 50% of cases
Remote Damage Control Resuscitation

- Why is Remote Damage Control Resuscitation so important?
  - Civilian setting – Trauma is the leading cause of death – 1 to 44 years of age
    - Trauma - #1 cause – Years of potential life lost
    - Trauma-induced coagulopathy and shock
      - Develop rapidly after severe injury
      - Associated with increased mortality
  - Imperative - Achieve
    - Improvement of pre-surgical management of trauma patients with uncontrolled major hemorrhage

Remote Damage Control Resuscitation

- Transfusions – Critical and essential part of RDCR
- Damage Control Resuscitation – Balanced transfusion therapy (e.g., 1:1:1 plasma: platelets: RBCs)
- Prehospital setting (austere environments)
  - Logistically difficult to provide RT platelets
  - Difficult to carry large numbers of blood products
  - We need to “think” and “practice differently
  - Cold WB and Cold platelets – More practical
The THOR group and the way (far) forward: transfusion medicine support is vital to the mission!

James R. Stubbs, MD

TRANSFUSION 2017;57:714-715

Low-Titer Cold-Stored Group O Whole Blood
Whole Blood

- World War II – US Forces established Field Blood Banks
  - Fresh whole blood – Collected from immediately available donors
  - Used immediately
- Low-titer Cold WB units - Delivered far forward – Resuscitation near point of wounding hundreds of thousands
- Korean War, and Vietnam War
  - “Low titer” threshold – Set in Korean War – 256
  - Vietnam
    - Plan - Early 1965 – Only low-titer group O whole blood
    - Blood requirements increased – December 1965 -First shipment of non-group O whole blood
    - Low titer group O whole blood – Only product in forward, pre-hospital settings

Trauma Care

- During and after Vietnam era
  - Crystalloids and colloids replaced blood – Primary resuscitative approach for hemorrhagic shock
    - Fear and risks of infectious disease transmission
      - Hepatitis and later HIV
  - Carrico CJ et al – Crit Care Med 1976; 4:46-54
    - Interstitial compartment required resuscitation with 1 to 2 liters of crystalloid for tissue perfusion
    - Transfusions only if hemodynamic instability persisted
    - Patients – Commonly received 5 to 10 liters of crystalloid before any blood products
      - Dilutional coagulopathy and severe interstitial edema
      - “Da Nang Lung” – Massive crystalloid resuscitation causing pulmonary edema
      - Era of acute respiratory distress syndrome, abdominal compartment syndrome, multi-organ failure, and anasarca in trauma patients in intensive care units
Trauma Care

- Moore and Shires – Annals of Surgery 1967; 166:300-301
  - “Blood should still be replaced during major operative surgery as it is lost. The use of salt solutions appears to be a physiological adjunct to surgical trauma, not a substitute for blood.”
- Shoemaker WC – Crit Care Med 1976; 4:71-78
  - Challenged interstitial compartment resuscitation
  - Emphasized – Whole blood for hematocrit < 30%
- Subsequent research (e.g. Makey AT et al – J Trauma 2010; 68:305-311)
  - Crystalloid-based resuscitation – Increased inflammation and vascular permeability

- Blood-based resuscitation – Back in fashion
- “Reconstituted whole blood” - Championed
  - Military – Iraq and Afghanistan
  - Civilian trauma centers –
    - Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) Trial
    - 1:1:1 or 1:1:2 ratios of plasma: platelets: and RBCs
      - Whole blood preferred over all other blood product combinations and fluids
Whole Blood

- Rationale
- WB – Provides RBCs, platelets, and plasma in physiologic proportions in one product


<table>
<thead>
<tr>
<th>Table 1. Comparison of “reconstituted” whole blood (1:1:1) to whole blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Reconstituted” whole blood (1:1:1)*</td>
</tr>
<tr>
<td>Total volume</td>
</tr>
<tr>
<td>Hematocrit</td>
</tr>
<tr>
<td>Platelet count</td>
</tr>
<tr>
<td>Coagulation factor activity</td>
</tr>
</tbody>
</table>

*Assumptions: PRBC hematocrit 55%, PLTs 5.5 × 10^11, FFP 80% coagulation factors.

Whole Blood

- 1:1:1 reconstituted whole blood
  - Each separate component – Increased volume of anticoagulant/preservative solution
    - Contribute to dilutional coagulopathy
  - Life-threatening bleeding
    - Shock and coagulopathy potentiate one another
      - Organ failure and death if not rapidly reversed
      - A balanced approach to shock and coagulopathy - Preferred
  - WB – Addresses shock and coagulopathy in one product
    - 30% higher oxygen carrying capacity than 1:1:1 ratio products
    - Better mitigation of oxygen debt
      - Prevents adverse effects of hypoxia
      - Hypoxia negatively impacts coagulation
    - Hemostatic function of platelets – Superior to RT platelets
Whole Blood units were stored for 21 days at either 4°C or 22 °C.

The in vitro hemostatic function of Whole Blood is better preserved by cold storage over 21 days.
Whole Blood

- Low titer group O WB safer than group-specific WB?
- Hemolysis - Passive anti-A or anti-B to group A, B, or AB recipients
  - Appears to be a rare event
  - ABO minor-mismatched platelet transfusions – “Routine” practice in oncology for a long time
    - Similar volume of plasma as WB units
    - “Passive” hemolysis – Mild-to-moderate
  - UK SHOT data – 1:120,000 minor incompatible platelet transfusions
- Group O Cold WB – Select low titer donors
- Massive transfusion patients – Group O RBCs

Whole Blood

- ABO group-specific RBCs or WB
  - Primarily due to human error
  - More uniformly severe reactions (more likely to be fatal)
  - 1:80,000 transfusions
  - Risk - Group-specific RBC-containing blood components
    - Amplified in the setting of massive transfusion and multiple severely injured patients
  - Current standard – Group-specific WB
    - Pose a higher risk than low titer group O WB????
Whole Blood

- Warm or cold low titer Group O whole blood
  - Accepted for combat operations – Several countries
    - United States
    - United Kingdom
    - France
    - Australia
    - Norway

Whole Blood

- Whole Blood - Civilian Institutions
  - Mayo Clinic
  - University of Pittsburgh
  - Kentucky Blood Centers
  - Norway
  - Israel
Whole Blood at Mayo Clinic
The Story Begins

- September 2013 – Transfusion Medicine - Request from Trauma, Critical Care, General Surgery (TCCGS)
  - ABO group-specific, leukocyte-reduced, platelet-preserved stored whole blood (SWB)
  - Resuscitation support of trauma patients
- Transfusion Medicine stakeholders meeting
  - Logistics
    - Collection, manufacturing, and provision of a “new” blood component for our cGMP facility
  - Further information requested from TCCGS
    - Anticipated number of SWB units required
Whole Blood

- TCCGS Information – Annual data
  - 50 to 70 massive transfusion episodes in trauma patients and 15 to 25 massive transfusion episodes in non-trauma patients (i.e., 65 to 95 TCCGS massive transfusion episodes)
  - Average RBC use per massive transfusion – 15 RBC units
  - Estimate – 975 to 1425 RBC units administered during TCCGS massive transfusions

Whole Blood

- 70% of massive transfusion RBCs transfused after recipient ABO/Rh determined
  - Estimate - 683 to 998 massive transfusion RBC units
  - If SWB use restricted to patients of blood group A or O – Estimate – 587 to 858 SWB units from male donors (TRALI mitigation) needed
ABO Group-Specific Whole Blood

- Concerns – Division of Transfusion Medicine
- Projected number – Group A and group O SWB units – Significant stress on the overall blood supply at our institution
- Fun with numbers!
- Total RBCs produced from Mayo Clinic Blood Donor Center in 2014
  - 23529
- Total group A and O RBCs produced from Mayo Clinic Blood Donor Center in 2014
  - 19524
- Estimated RBCs from Group A and Group O males in 2014
  - 9,762
  - If 10% of these donations are rerouted to Whole Blood – Significant impact on overall supply of group O RBCs for Mayo Clinic (14-day product from donors with an 84-day interdonation interval)

ABO Group-Specific Whole Blood

- Massive transfusions – Unpredictable
  - Can’t reliably plan for when they will occur
  - Can’t predict the extent of individual blood product demands on the system
- Concerns – Inventory management
  - Maintaining an adequate supply of group A and O SWB
  - Preventing an excess of SWB which can only be used for a limited recipient base for a 14-day period
ABO Group-Specific Whole Blood

- Donor availability concerns + Concerns about matching of supply and demand (i.e., the product actually being there and rapidly available when really needed without drowning in SWB outdates)
- Mutual agreement – TCCGS and Transfusion Medicine – Abandon the idea of group-specific SWB for resuscitations

ABO Group-Specific Whole Blood

- Alternative plan – Blood group O “universal donor” SWB!!!!
- Major obstacle - AABB Standards do not acknowledge universal donor Whole Blood
- Variance needed – AABB Standards Program Unit (SPU)
AABB Standards 28th Edition

• 5.25 - Urgent Requirement for Blood and Blood Components
  • “The blood bank or transfusion service shall have a process for the provision of blood and blood components before completion of tests listed in Standards.............when a delay in transfusion could be detrimental to the patient.”
  • 5.25.1 – “Recipients whose ABO group is not known shall receive group O Red Blood Cells.”

AABB Standards 28th Edition

• 5.14 – Selection of Compatible Blood and Blood Components for Transfusion
  • 5.14.1 – “Recipients shall receive ABO group-specific Whole Blood or ABO group-compatible Red Blood Cell Components.”
The state of the science of whole blood: lessons learned at Mayo Clinic

James R. Stubbs,1 Martin D. Zielinski,2 and Donald Jenkins2

TRANSFUSION 2016;56:S173–S181

Disturbing Information

Amplitude by Collagen(ohm)

<table>
<thead>
<tr>
<th>Sample</th>
<th>Agitate</th>
<th>No Agitate</th>
</tr>
</thead>
<tbody>
<tr>
<td>5FWB0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5SWB0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5SWB1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5SWB2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5SWB3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5SWB7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Agitate
- No Agitate
Group O Whole Blood
New Approach

- Non-leukocyte filtered SWB – Retain platelet function for 14 days or longer
- Strong desire on part of TCCGS Service – explore the potential benefits of SWB for in-hospital and potentially remote damage control resuscitations (blood far forward)
- New approach
  - Utilize SWB in same manner and utilize most of the processes established for the leukocyte-depleted, platelet-preserved SWB
  - Whole Blood – Collected in collection sets normally used for the manufacture of our other products (RBCs, plasma etc.)
  - Named Trauma Whole Blood (T-WB) in our system
  - T-WB - Stored in the refrigerator in unmanipulated state and it will be administered via a standard infusion set

Group O Whole Blood
New Approach

- Issues we had to “wrestle” with as it pertains to a non-leukocyte reduced product
  - Not a CMV-safe product – Should we collect only from CMV-negative male group O donors?
    - Decision by TCCGS service – CMV-negative products not required
Group O Whole Blood

New Approach

- Issues we had to “wrestle” with as it pertains to a non-leukocyte reduced product
  - Transfusion-associated graft-versus-host disease (TA-GVHD) – Should these SWB products be irradiated?
    - Closest irradiators – 6 blocks from the Saint Marys Hospital Transfusion Laboratory
    - Irradiate on demand? – Logistical nightmare of tubing blood products back and forth from Saint Marys to Methodist Hospital or the Hilton Building for irradiation during a resuscitation – Time delays and logistical issues (losing products in the tube system) – No
    - Irradiate and store – Concerns about potassium levels rising in stored product - No

Group O Whole Blood

- AABB Variance Request – October 8, 2015
- Standards for Blood Banks and Transfusion Services 29th Edition
- GRANTED
- “The BBTS SPU reviewed your request to amend your original variance request to include group O non-leukocyte reduced platelet-preserved whole blood as universal donor units for use in trauma victims when the recipient’s ABO group is not known. The SPU agreed with this plan and has approved your request at this time.”
Group O Whole Blood Guidelines

- Adult Practice Management Guideline – Trauma, Critical Care & General Surgery (TCCGS)
  - Policies (Continued)
    - Whole blood components will be stored in the Transfusion Laboratory and not in remote locations such as the Emergency Department refrigerator
    - Four group O whole blood units (two O positive and two O negative) from male blood donors with anti-A and anti-B titers < 200 will be kept in inventory for the whole blood resuscitation protocol

- No more than 2 whole blood units may be transfused to any patient unless the patient has been confirmed to be blood group O as performed by the Mayo Clinic ABO grouping process
- Transfusion team nursing personnel will respond to Level I trauma activations as per standard practice.
- If further blood product resuscitation is required the Institutional Massive Blood Transfusion Protocol is activated
Group O Whole Blood
New Approach

• What the heck are we doing?
• Rolling out stored T-WB in November 2015
• Two key questions
  • Is non-leukocyte-reduced universal donor stored SWB safe?
  • Is SWB a preferable option for resuscitation (DCR and RDCR) of trauma patients (i.e., does it actually work better than blood component therapy)?
• This SWB practice is going to most closely resemble the military experience during World War II, the Korean War, and the Vietnam War
  • Low-titer, Group O, non-leukocyte-reduced SWB is safe
  • Is SWB better than components? That question has not been answered satisfactorily yet!!!! – But we will never know the answer unless we try!

Cold- Stored Apheresis Platelets
Trauma and Trauma Patients

- Platelet transfusions – Improved outcomes
- Military conflicts – Afghanistan and Iraq
  - Early platelet transfusions – Beneficial
- Platelet issue in such patients - Not hypoproliferative thrombocytopenia
- Platelet needs - Complex trauma-induced condition
  - Platelet consumption and loss
  - Platelet dysfunction
- Purpose of platelet transfusions
  - Not prolonged post-transfusion survival
  - Rapid hemostatic control
    - Recovery of platelet count
    - Relatively short time period - Patients’ own platelets

Ten-year analysis of transfusion in Operation Iraqi Freedom and Operation Enduring Freedom: Increased plasma and platelet use correlates with improved survival

Heather F. Pidcoke, MD, James K. Aden, PhD, Alexandra G. Mora, Matthew A. Borgman, MD, Philip C. Spinella, MD, Michael A. Dubick, PhD, Lorne H. Blackbourne, MD, Andrew P. Cap, MD, PhD

**BACKGROUND:** The Joint Theater Trauma Registry database, began early in Operation Iraqi Freedom and Operation Enduring Freedom, created a comprehensive repository of information that facilitated research efforts and produced rapid changes in clinical care. New clinical practice guidelines were adopted throughout the last decade. The damage control resuscitation clinical practice guideline sought to provide high-quality blood products in support of tissue perfusion and hemostasis. The goal was to reduce death from hemorrhagic shock in patients with severe traumatic bleeding. This 10-year review of the Joint Theater Trauma Registry database reports the military’s experience with resuscitation and coagulopathy, evaluates the effect of increased plasma and platelet (PLT) to red blood cell ratios, and analyzes other recent changes in practice.

**METHODS:** Records of US active duty service members at least 18 years of age who were admitted to a military hospital from March 2003 to February 2013 were entered into a database. Those who received at least one blood product (n = 3,632) were included in the analysis. Data were analyzed with respect to interactions within and between categories (demographics, admission characteristics, hospital course, and outcome). Transfusions were analyzed with respect to time, survival, and effect of increasing transfusion ratios.

**RESULTS:** Coagulopathy was prevalent upon presentation (37% with international normalized ratio ≥ 1.5), correlated with increased mortality (fourfold higher), and was associated with the need for massive transfusion. High transfusion ratios of fresh frozen plasma and PLT were associated with higher survival but did not decrease blood requirement. Survival was most correlated with PLT ratio; but high fresh frozen plasma ratio led to an additive effect (PLT odds ratio, 0.22).

**CONCLUSION:** This 10-year evaluation supports earlier studies reporting the benefits of damage control resuscitation strategies in military casualties requiring massive transfusion. The current analysis suggests that deficits in PT/INR function may contribute to coagulopathy of trauma. (J Trauma Acute Care Surg. 2012;73: S145–S152. Copyright © 2012 by Lippincott Williams & Wilkins)

**LEVEL OF EVIDENCE:** Epidemiologic study, level IV

**KEY WORDS:** Transfusion ratios, coagulopathy, massive transfusion, OIF, OEF
Trauma and Trauma Patients

- RDCR – Blood availability limited
  - Type and number of blood components available
  - Storage conditions
    - Room temperature platelets (RT-PLTS)
      - Not considered practical – Prehospital transfusions
      - Blood transport containers (i.e. coolers) – Limited number of RBCs and in some cases thawed plasma
      - Deprives trauma victims – Crucial part of early hemostatic therapy – platelet transfusions
    - If platelets are to be effectively added to RDCR
      - “New” thinking

Platelets

- Historically - Major indication for platelet transfusions
  - Hypoproliferative thrombocytopenia– Cancer and cancer treatment
- Focus – Regulatory and accrediting agencies
  - \textit{in vivo} platelet recovery and survival
  - Platelet function – Adhesion and aggregation
    - Not received equal consideration
    - Determination – Optimal storage considerations
Platelets

• Current AABB Standards
• Accepted standard for storage
  • Room temperature (20°C to 24°C)
  • Constant agitation
  • Maximum duration – 5 days
• Storage conditions
  • Maximize in vivo recovery and survival of transfused platelets

DHHS 2011 National Blood Collection and Utilization Report
Platelets

- Refrigerated storage (CS-PLTS) – Not new!
- 1960s to mid-1980s – CS-PLTS were a standard
- In fact…….CS-PLTS still in compliance with……

For treatment of hemorrhage, platelet activity may be more important than recovery and survival.
Platelets

- Effects of refrigerated storage
  - Actin polymerization
  - Disassembly of microtubules
  - Increase in cytosolic calcium
  - Shape change
- Despite such changes – Compared to RT-PLTS
  - Enhanced
    - Aggregation
    - Adhesion
    - Clot strength
- CS-PLTS – “Primed” to rapidly participate in hemostasis following transfusion
  - 2–3 day post-transfusion circulation time – Long enough to contribute to hemostasis in bleeding patients

Apheresis platelets stored at 4°C are hemostatically more effective than apheresis platelets stored at room temperature over 5 days.
Cold stored platelets may support faster hemostasis for acute bleeding

Effect of cold storage on shear-induced platelet aggregation and clot strength

Pradee M. Nair, MS, Heather E. Pidcocke, MD, PhD, Andrew P. Cap, MD, PhD,
and Anand K. Ramasubramanian, PhD, San Antonio, Texas

BACKGROUND: Platelets (PLTs) participate in hemostasis and survivals following trauma. PLTs for transfusion are maintained at room temperature (RT, 22°C), limiting viability to 5 days because of metabolic compromise and high risk of bacterial contamination. RT storage may result in weaker clot, delay hemostatic control, whereas cold storage (4°C) could permit longer PLT shelf life and reach in a more hemostatic product. In this study, we characterized the effect of storage temperature on shear-induced PLT aggregation, clot formation, and strength.

METHODS: PLTs obtained from phlebotomized blood or byapheresis were stored at RT or 4°C for 5 days, and PLT aggregation and clot strength were assessed at 37°C. We studied PLT aggregation at steady and complex patterns of shear rates (500-2,500 per second) by floe cytometry, and the kinetics of clot formation and strength were measured using turbidity and dynamic mechanical analysis, respectively.

RESULTS: PLT aggregation was higher in CS-stored samples on D5 compared with fresh or RT-stored samples at all shear rates tested (both VS. 4°C and RT vs. 4°C, p < 0.05). PLTs stored at 4°C for 5 days formed significantly stronger clots compared with fresh or RT-stored samples as quantified by turbidity and elastic modulus measurements (fresh vs. 4°C and RT vs. 4°C, p < 0.05).

CONCLUSION: Our results show that cold-stored PLTs are more responsive to aggregation stimuli and form stronger clots, presumably because of thicker fibrin strands. These data suggest that the superior functionality of cold-stored PLTs may support faster hemostasis for acutely bleeding in trauma patients compared with RT-stored PLTs. J Trauma Acute Care Surg. 2014;77: 588–593. Copyright © 2014 by Lippincott Williams & Wilkins.

KEY WORDS: Platelet storage; refrigeration; SPS; clot strength; hemostasis.

Cold-Stored Platelets – Clinical Studies

- Small number – Supporting refrigeration
- J Lab Clin Med 1978; 91:618-624
  - CS-PLTS better corrected the bleeding time versus RT-PLTS
- Transfusion 1973; 13:61-68
  - CS-PLTS better corrected the bleeding time in aspirin-treated adults than RT-PLTS
Comparison of the Hemostatic Effects of Fresh Whole Blood, Stored Whole Blood, and Components After Open Heart Surgery in Children

By Catherine S. Mannix, Kuhleen W. Heidberg, Haewon C. Kim, Greta R. Burn, Susan Nicole, Daniel Jobes, Elias Schwartz, and William I. Norwood

In a double-blinded study, we compared the postoperative (post-op) blood loss in 181 children undergoing open heart surgery with cardiopulmonary bypass whose immediate post-operative transfusion requirements were met with either fresh whole blood (FPWB), 24- to 48-hour-old whole blood or reconstituted whole blood (packed red blood cells, fresh frozen plasma (FFP), and platelets). Assignment to treatment groups was not strictly random but dependent, in part, on the need for emergency or routine transfusions. The three groups were comparable with respect to patient age, pre-operative coagulation profiles (bleeding time, prothrombin time, activated partial thromboplastin time, platelet count, fibrin split products, fibrinogen, and platelet aggregation tests), difficulty of operative procedures and time spent on CPB. Mean 24-hour post-op blood loss in milliliters per kilogram was 90.3 ± 3.3 in the FPWB group, 46.8 ± 6.0 in the 24- to 48-hour-old group, and 74.2 ± 9.9 in the reconstituted group (P = .03). When blood loss was compared in the 93 children less than 2 years of age, mean blood loss was 52.3 ± 10.8 in the FPWB group, 51.7 ± 7.4 in the 24- to 48-hour-old group, and 49.2 ± 10.7 in the reconstituted group (P = .001). For subjects who had received reconstituted blood, 30-minute and 1-hour post-op platelet agglutination responses to adenosine diphosphate (10 μmol/L) and 30-minute aggregation response to epinephrine (2.5 μmol/L) were more depressed than in the FPWB and 24- to 48-hour groups (P < .001, P = .005, and P = .02). Comparison of other post-op coagulation tests could not explain the increased blood loss in the reconstituted group. We conclude that the transfusion of 24- to 48-hour-old whole blood is associated with significantly less post-op blood loss than the transfusion of packed red blood cells, FFP, and platelets in children under 2 years of age undergoing open heart surgery. The blood losses associated with the transfusion of FPWB and 24- to 48-hour-old blood are comparable and may be, in part, due to better functioning platelets.

© 1991 by The American Society of Hematology.

Cold-Stored Platelets

- 2013 – Potential added value in bleeding patients
- Joint decision – Trauma and Transfusion Medicine – Mayo Clinic, Rochester
- Pursue and obtain
  - Regulatory and Accreditation approvals
  - Use CS-PLTs in our trauma practice
Cold platelets for trauma-associated bleeding: regulatory approval, accreditation approval, and practice implementation—just the “tip of the iceberg”

James R. Stubbs,1 Sheryl A. Tran,2 Richard L. Emery,1 Scott A. Hammel,1 De Anna L. Haugen,2 Martin D. Zielinski,4 Scott P. Ziellow,4 and Donald Jenkins4

TRANSFUSION 2017

CS-PLTS - Approval

• March 27, 2015 – FDA response
  • “We have approved your request to include an alternative procedure from 21 CFR 610.53(c) and 606.65(e) under the provisions of 21 CFR 640.120 to store apheresis platelets at refrigerator temperature without agitation for up to 3 days. You will restrict the use of these cold-stored platelets to use in the resuscitation of actively bleeding patients.”
CS-PLTS - Approval

• AABB Letter – October 8, 2015
  • “The BBTS SPU reviewed your request for variance and has elected to grant your request. The approval of the variance however is limited to 1°C to 6°C stored platelet components as indicated below:
    • Standard 5.1.5.1 for bacterial detection testing for these platelet components.
    • Standard 5.1.8A for storage, allowing these platelet components to be stored at 1°C to 6°C without agitation for a maximum of 3 days.

• The variance applies only to apheresis platelet components collected using your automated blood collection systems and intended for use in the resuscitation of actively bleeding trauma patients as defined by your facility.
• These components may be stored for a maximum of 3 days at 1-6°C without agitation.
• Use is restricted only to the resuscitation of actively-bleeding trauma patients.
• These components shall not be released to the general transfusable inventory.”
BLEEDING & THROMBOSING DISEASES / CONFERENCE & WORKSHOP

CS-PLTS - Implementation

- Goal – Collect 3 group A CS-PLTs per week
- Major challenge – Product wastage
  - 3-day storage – Tight window
    - Quarantine 12-18 hours until infectious disease testing complete – True availability – About 2 days
  - Clot formation
    - Plasma-rich platelets – Like to clot in the refrigerator
      - Fibrinogen + Glycoprotein IIb-IIIa (GP IIb-IIIa)

BLEEDING & THROMBOSING DISEASES / CONFERENCE & WORKSHOP

CS-PLTS - Implementation

- Major challenge – Product wastage
  - October 2015 thru August 2016 - 119 CS-PLTs produced
    - Nine discarded prior to distribution to Transfusion Laboratory (definitive or suspected clots)
    - 110 delivered to Transfusion Laboratory
      - 21 (19.1%) transfused
      - 89 (80.9%) discarded
        - 20 developed clots
        - 65 expired
        - One returned after issue and expired
        - One stopped due to a suspected transfusion reaction
        - Two lost due to transport failure of pneumatic tube system
Storage of platelets at 4°C in platelet additive solutions prevents aggregate formation and preserves platelet functional responses

Todd M. Getz, Robbie K. Montgomery, James A. Bynum, James K. Aden, Heather F. Pidcocke, and Andrew P. Cap

Background: Platelet (PLT) storage has been limited to 5 days at room temperature due to metabolic decline and risk for bacterial contamination. Refrigeration preserves PLT metabolism and function as well as limits bacterial growth; however, cold storage of PLTs also leads to aggregate formation. We hypothesized that storage of PLTs concentrated at 4°C leads to glycoprotein IIb/IIIa activation and aggregate formation through fibrinogen binding and that this could be prevented by storing PLTs in PLT additive solution (PAS) without compromising PLT function.

Study design and methods: Apheresis PLTs in plasma (AP) or apheresis PLTs in PAS were stored at 22 or 4°C for up to 15 days. Measurements include PLT counts, blood gases, aggregation response, flow cytometry analysis of integrin levels, activation markers, and microparticle formation.

Results: Storage of AP at 4°C led to a gradual decline in PLT count and an increase in aggregate formation that was mediated by intracellular Ca2+ leak and fibrinogen receptor activation. Storage of PAS at 4°C prevented aggregate formation due to dilution of plasma fibrinogen. PAS stored at 4°C maintained aggregation responses to multiple agonists better than 22°C controls.

Conclusion: Storage of AP at 4°C leads to low-level GP IIb/IIIa activation and results in aggregate formation over time. Separating the PLTs from the plasma component and storing them in PAS at 4°C resolves aggregate formation and preserves the metabolic and functional responses of these stored PLTs.

Storage of apheresis platelets at 4°C in platelet additive solution prevented aggregate formation due to dilution of fibrinogen and maintained aggregation responses to multiple agonists better than platelets stored at 22°C.
CS-PLTS - Future

- Next major issue – Bacterial contamination
  - Refrigerated storage – minimizes bacterial growth
    - 5-day CS-PLTs should be as safe or safer than 5-day RT-PLTS
  - Pathogen Reduction + Platelet Additive Solution
    - Allow storage of at least 10 days
    - Impact – Stretch way beyond trauma
    - Product of choice for all actively bleeding patients?
- Practical alternative to RT-PLTS is in reach!
- 3-day CS-PLTS – “Tip of the Iceberg!”
Remote Damage Control Resuscitation Goal

- Air Ambulance Cooler (Rotor Wing Aircraft)
  - 2 O Negative RBC Units
  - 2 Group A Thawed Plasma Units
  - 1 Low-Titer O Negative Cold-Stored Whole Blood Units
  - 1 Group A Cold-Stored Platelet Unit
- Will this make a difference in civilian trauma care?
  - Too early to know for sure
  - Cold-Stored Platelet and Cold-Stored Whole Blood outcome studies - Ongoing

Helicopter Blood Transport

- 2 RBCs, WB, and 1 FFP in a row
- 1 FFP on the side
- Flattened Cold Platelet on top (with part tucked on side with FFP)
Thank You!