What’s COLD is Hot Again!

Back to the Future with Whole Blood

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LifeStream Transfusion Medicine Forum
March 9, 2019
Objectives

• Describe historical use of whole blood
• Outline current impetus for using whole blood in trauma settings
• Describe potential challenges for implementation
Whole Blood

Gimme some whole blood!

WHADDYA MEAN, WHOLE BLOOD?

Definitions Matter!
Whole Blood

8 hours RT

Warm, fresh

Unmodified
Untested

Cold, stored

21-35 days
1-6C

Low-titer
ABO abs

Leukoreduced but platelet-rich
Familiar?

Whole blood donation
500 mL

Packed red blood cells
200 mL + 100 mL ADSOL
Shelf life: 42 days at 1-6°C

Platelet rich plasma
300 mL

Platelets
50 mL
Shelf life: 5 days at room temperature

Plasma
250 mL
Fresh frozen plasma: Frozen within 8 hours of collection
FP24: Frozen within 24 hours of collection
Shelf life: 1 year at -18°C

Cryoprecipitate
15 mL
Shelf life: 1 year at -18°C
Component Therapy
Does This Work?
History

Jean Denis 1600s

Through 1960s-70s
Military Use of WB

- All conflicts of 20th/21st Centuries
  - WWI
  - WWII
  - Korea
  - Vietnam
  - Iraq
  - Afghanistan

“WB Era”

“CT Era”
Whole Blood in Korea/Vietnam

• In both conflicts, cold-stored whole blood used extensively
• Military policy:
  • Whole blood must be group O
  • Whole blood must be “low titer”
Group O WB-Historical

Whole Blood MUST Be ABO-identical

DONOR

RECIPIENT

Anti-A

Anti-B
What’s a “Titer?”

Donor A: High Titer: Stronger Ab More Risk?

Donor B: Low Titer: Weaker Ab Less Risk?
So, How Did it Go?

• Korean Conflict:
  • Over 400,000 group O WB transfusions
  • No acute hemolysis

• Vietnam Conflict
  • Over 230,000 group O WB transfusions
  • 1 acute hemolysis
  • “High titer” unit given in error
Military Use Today

• In Iraq and Afghanistan:
  • Cold whole blood used
  • Fresh whole blood used
  • Component therapy (1:1:1 DCR ratio) used
  • Safety has been reported, though not prospectively studied
    • Multiple reports of better survival
What’s Behind the Current Interest?

- History already mentioned
- Simplifies logistics
- More concentrated
- Leukoreduction is possible
- Cold-stored platelets: Better?
- Preliminary data: No hemolysis
Which Would You Rather?

OR
Logistical and Administrative Benefits of WB

6 + 6 + 1 + 1 = 14 or 5?
WB makes it easier to provide balanced resuscitation

- Time from ED admission until administration of WB (n=16) or at least 1 RBC, plasma, and PLT in historical cohort (n=50)
Concentrate, Please!

70 mL AC/bag

~125 mL AC-preserv/bag

~50 mL AC/bag

35 mL AC/bag

6 units WB: 420 mL “clear fluid”

6:6:1: ~1080 mL “clear fluid”

After Spinella PC, J Trauma 2009:S69-76
Contributions to Hemostasis

1:1:1 is not the same as WB

Platelet count contribution $10^9/L$

- Normal Blood
- Fresh WB in CPD $\sim 40\%$ Hct
- $1:1:2$ MTP
- $1:1:1$ MTP $\sim 30\%$ Hct

Effective plasma coagulation activity (U/mL)

Image courtesy Dr. Mark Yazer

BBGuy.org
Leukoreduction

- “Whole Blood cannot be leukocyte reduced”
- Traditional LR filters remove WBCs AND PLTs
- Possible problems:
  - Febrile reactions
  - HLA alloimmunization
  - CMV transmission
  - Decreased RBC alloimmunization?
  - Immunosuppression?
Leukoreduction Upgrade

New PLT-sparing LR Filter
Platelets with a Chill

• Traditional blood banking dogma:
  • Platelets are better when stored at warm temperatures (20-24C) than at 1-6C
  • Platelets “activate” at colder temps
  • Platelets are cleared faster after storage at colder temps
"Cold" (1-6°C)

- Activated
- Lose round shape
- Cleared faster

"Warm" (20-24°C)

- Less activated
- Rounder
- Cleared slower

Activated PLTs Removed
What’s the Goal?

Keep count higher longer

“Warm” (20-24C)

Stop bleeding NOW!

“Cold” (1-6C)
OK, So Do Cold Platelets WORK?

• Cold platelets appear more hemostatically active
• All in-vitro measures show greater function
• Function lasts 10-14 days
• Concern for TOO MUCH activity in past

Image: Becker GA et al, Transfusion 1973!
Conclusions

- "Cold" platelets in LTOWB might work just great
- Quantity is about what we used to expect from one unit of "whole blood-derived" platelets
  - Roughly 1/5 to 1/6 of an apheresis PLT dose
But What About Those Missiles?

- As mentioned, WB must be ABO-identical due to concerns about hemolysis from plasma
- BUT...
  - Blood banks cross ABO plasma lines every day!
  - AND
  - Group A plasma now very common in MT
Platelet Transfusions

Group A Donor

Group B Recipient

Meh!
Group A Plasma Safe for MT

Incompatible type A plasma transfusion in patients requiring massive transfusion protocol: Outcomes of an Eastern Association for the Surgery of Trauma multicenter study

W. Tait Stevens, MD, Bryan C. Morse, MS, MD, Andrew Bernard, MD, Daniel L. Davenport, PhD, Valerie G. Sams, MD, Michael D. Goodman, MD, Russell Dumire, MD, Matthew M. Carrick, Patrick McCarthy, MS, James R. Stubbs, MD, Timothy A. Pritts, MD, PhD, Christopher J. Dente, MD, Xian Luo-Owen, PhD, Jason A. Gregory, MD, David Turay, MD, PhD, Dina Gomaa, Juan C. Quispe, MD, Caitlin A. Fitzgerald, MD, Nadeem N. Haddad, MD, Asad Choudhry, MD, Jose F. Quesada, MD, MS, and Martin D. Zielinski, MD, Lexington, Kentucky

120 B and AB Patients: No Hemolysis
No evidence of poor outcome
Group A Plasma Safe for MT

**Original Research**

Safety of the use of group A plasma in trauma: the STAT study

Nancy M. Dunbar¹ and Mark H. Yazer,² on behalf of the Biomedical Excellence for Safer Transfusion (BEST) Collaborative and the STAT Study Investigators³

354 B and AB Patients: No Hemolysis
No evidence of poor outcome

Dunbar NM et al, Transfusion 2017;57:1879-1884
BUT, Rarely...

Group O Donor

Group A Recipient

A A A A A

OUCH!
Thus, the “LT”

• This possible interaction is what has scared blood bankers for decades
• VERY uncommon in general
• EVEN MORE uncommon if the plasma is screened
• “Low-Titer” is in the eye of the beholder
“Critical" Titer

0.5 ml transferred from tube to tube

Discard

0.5 ml

1
2
3
4
5
6
7
8
9
10

1:2 1:4 1:8 1:16 1:32 1:64 1:128 1:256 1:512

Pittsburgh

US Military

Common
LTOWB Defined in Pittsburgh

- O pos (except women below age 50)
- Male-only donors (TRALI)
- 21 day shelf life at 1-6°C
- Only used for 14 days
- Anti-A/anti-B titer <50
Sounds Simple...

• Is everything sunny and rosy?
• Well...

• Main Objections:
  • Civilian data is very limited so far
  • It is NOT just a simple change for blood collectors
Where’s the Data?

**Results**
- 27 non-group O recipients
- 2 units maximum
- No significant differences in hemolysis markers
- No evaluation of outcomes

*Transfusion Medicine, Feb 2017*
Hemolysis Markers

Seheult J et al. Transfusion Medicine 2017;27:30-35
Where’s the Data?

Results

- 102 non-group O recipients
- 1-4 units maximum (23 got 3-4 units)
- No significant differences in hemolysis markers
- No clinical reactions
- No reporting of outcomes

Original Research

Safety profile of uncrossmatched, cold-stored, low-titer, group O+ whole blood in civilian trauma patients

Jansen N. Seheult,1 Marshall Bahr,2 Vincent Anto,3 Louis H. Alarcon,4,5 Alain Corcos,4,5 Jason L. Sperry,4,5 Darrell J. Triulzi,1,6 and Mark H. Yazer1,6

Transfusion, May 2018
Hemolysis Markers

Seheult J et al. Transfusion 2018; Early View (June 2018)
Where’s the Data?

**Results**

- 47 LTOWB recipients (30 non-O) in one center
- 2 units maximum
- No significant differences in outcomes vs CT
- Limited by design

**Initial safety and feasibility of cold-stored uncrossmatched whole blood transfusion in civilian trauma patients**

Mark H. Yazer, MD, Byron Jackson, MD, Jason L. Sperry, MD, Louis Alarcon, MD, Darrell J. Triulzi, MD, and Alan D. Murdock, MD. Pittsburgh, Pennsylvania

*J Trauma Acute Care Surg, 2016;81:21-25*
Where’s the Data?

Results

- 135 LTOWB recipients (all groups) in one center
- 4 units maximum
- No significant differences in outcomes vs CT
- “Trends” toward better mortality and lower lactates

Clinical outcomes among low-titer group O whole blood recipients compared to recipients of conventional components in civilian trauma resuscitation

Jansen N. Seheult,1 Vincent Anto,2 Louis H. Alarcon,3,4 Jason L. Sperry,3,4 Darrell J. Trudzi,4,5 and Mark H. Yazer4,5

Transfusion, August 2018
What Do We KNOW Now?

- Whole blood has a long history of “safe” use
  - BUT how closely have people looked?
- Some military studies show survival benefit
  - BUT most military studies are FWB-based
- Early civilian data shows no evidence of hemolysis when non-O recipients get LTOWB
  - BUT we are still talking 100-200 patients or so
What Do We KNOW Now?

- It definitely CAN be done logistically
  - BUT it isn’t easy
- Early outcome studies: No harm
  - BUT no randomized studies yet
Well, What About the Blood Center?

- LTOWB is NOT the whole blood we currently collect
  - Different bag system entirely
  - Different leukocyte reduction filters
  - Different processing and management
  - 20-25% of donors will test as high titer
Dirty Little Secrets

• Vast majority of LTOWB collected in Pittsburgh is NOT used as LTOWB!
• Hospital TS operated by blood center
• LTOWB returned at 14 days
  • O+ RBCs made with 7 days shelf life
  • Plasma wasted
What We Are Doing

- Currently validating new bag and filters
- Complex cost structure
  - Lost potential products
  - Lost revenue
- Evaluating data coming from randomized trials
- Working with hospitals to evaluate desire to proceed
Resources

• BBGuy Essentials Podcast ([BBGuy.org/podcast](http://BBGuy.org/podcast)):
  • Episode 40CE: Whole Blood in Trauma
  • Episode 36: Group A Plasma in Trauma

• EMCrit Podcast:
  • Episode 202: Blood Bank Essentials
It’s never the wrong time to do the right thing

Joe Chaffin, MD