

I. Dating of Irradiated Red Blood Cells

Issue Summary
Blood Products Advisory Committee
July 22, 2004

Topic I: Dating Period for Gamma Irradiated Red Blood Cells (RBC)

Issue:

Current guidance permits a dating period for irradiated red blood cells (RBC) up to 28 days from the date of irradiation. However, recent data suggest that RBC recovery may drop below an acceptable level under some storage and irradiation conditions that are consistent with the current guidance. FDA seeks the advice of the Committee on a proposed revised standard for dating of gamma irradiated RBC.

Background:

Graft vs host disease can occur when viable cytotoxic allogeneic lymphocytes are transfused along with red blood cells (RBC) to immunosuppressed individuals who are unable to reject the lymphocytes. Once the allogeneic lymphocytes are present in the host they can attack any cell that expresses foreign HLA antigens. The symptoms appear 2-30 days post transfusion and include skin rash, diarrhea, liver enzyme elevation and pancytopenia. The frequency of occurrence is approximately 0.1 – 1% of all transfusions. Unfortunately there is no current therapy and mortality is as high as 80-100%. The patients at risk include neonates, individuals who are immunosuppressed from genetic disease or chemotherapy, and bone marrow or organ transplant recipients.

Fortunately graft vs host disease can be prevented by gamma irradiation of transfusion products. Gamma irradiation inactivates lymphocytes that cause the disease. However, irradiation also damages the RBC as evidenced by a potassium leak during storage and decreased viability (ability to circulate post transfusion). This damage requires limitation of the storage period for irradiated RBC. The current AABB Technique Manual and FDA recommendations suggest that the dose of gamma irradiation should be 2500 cGy to the center of the product. The shelf life limitations are found in the FDA 2000 guidance on licensure. It states:

The dating period for irradiated RBC should not be more than 28 days from the date of irradiation, but should not exceed the dating period of the original product.

The dating period specified under FDA's current guidance allows irradiation of the product anytime during storage, with storage up to 42 days if irradiation occurs on day 14 or later. This issue has received attention in the past and in fact was the subject of a 1992 NIH/NHLBI workshop and BPAC discussion in October 1994.

Discussion:

The data on viability of RBC post irradiation is limited. Dr. Gary Moroff published his studies in *Transfusion* in 1999 (1). More recently FDA reviewed data from 2 manufacturers who evaluated the effect of irradiation of RBC collected and stored in novel anticoagulants, ACD-A/AS-1 and ACD-A/AS-3. The collective results of these studies suggest that although irradiation of fresh RBC has minimal effects on viability, irradiation of RBC at 14 days after collection with subsequent storage out to 42 days leads to lower viability of the RBC.

FDA evaluates RBC products by their ability to circulate after transfusion in radiolabelled studies. Recovery of > 75% of radiolabeled RBC 24 hours after infusion into autologous donors has been the accepted FDA standard for all RBC products. The following statistical criteria are applied:

For radiolabeling studies FDA requests that studies be performed in at least two separate centers with 20-24 healthy donors combined total. The mean recovery should be $\geq 75\%$ with SD $< 9\%$ and with the 95% lower confidence limit for the mean $> 70\%$.

The data that will be presented in this session will indicate that additional limitations on the storage and dosage of irradiation should be applied to gamma-irradiated RBC.

1. Published data from Moroff et al (to be presented at the meeting) suggest that irradiation can be applied from day 1 to day 26 without a decrease in viability if the products are stored only to day 28 post collection. However, irradiation on day 14 and storage out to day 42 produces RBCs that do not meet the >75% criterion.
2. The following analyses are in reference to more recent data from two manufacturers (see attached tables):
 - a. Data from Manufacturer A on irradiated leukocyte reduced RBC showed:
 - Combining the results from all three centers, the mean percentage of radiolabeled RBC in vivo recovery for products irradiated on Day 1 and stored for 28 days was 80.7%, with a lower 95% confidence limit on the mean of 78.1%.
 - Combining the results from all three centers, the mean percentage of radiolabeled RBC in vivo recovery for products irradiated on Day 14 and stored for 28 days to day 42, was 77.6%, with a lower 95% confidence limit on the mean of 74.8%.

Individually all 3 centers met the 75% cutoff with day 1 irradiation and storage to 28 days. For day 14 irradiation and storage to 42 days, site 3 data had a mean and SD of 71.5 +/- 7.5 while site 1 and 2 had averages above 75% (At site 3, the irradiation dosage was 3000 cGy in comparison to site 1 and 2 where it was 2500 cGy). Thus site 3 results do not meet the

criteria while data from site 1 and 2 do not have sufficient number of donors to meet the statistical criterion used to evaluate these studies. Thus these data do not support irradiation on day 14 and storage out to 42 days.

- b. Data from Manufacturer B on irradiated leukocyte reduced RBC shows:
- Mean percentage of radiolabeled RBC in vivo recovery for products irradiated on Day 14 at 2500 cGy in two different centers and stored for 28 days to day 42, was 80.75, SD < 9. This study included a control arm of anticoagulant/storage solution that is already on the market.

Results at Site One:

- 12 TA (test), 12 WB (control, Teruflex Blood Bag System with AS-5, Terumo; BPF4 Pall for filter)
- In vivo RBC recovery:
 - For TA, 4/12 < 75%, mean = 75.63, SD = 7.65.
 - For WB 7/12 < 75%, mean = 72.51, SD = 6.97.

Results at Site Two

- 12 TA (test), 12 WB (control, Baxter Code 4R3433NM with AS-1; Sepacell RS-2000 for filter)
- In vivo RBC recovery:
 - For TA, 1/12 < 75%, mean = 85.9, SD = 8.
 - For WB, 3/12 < 75%, mean = 78.9, SD = 8.9

The test combinations in the above study met the criterion of recovery >75% however the control arm of the study at Site 1 failed the criterion.

Conclusion:

Based on the presented data FDA proposes to change the storage limits of gamma-irradiated RBC. We propose that RBC can be irradiated any time between day 1 and day 26 and stored out to day 28-post collection. RBC irradiated after day 26 to day 42 should be stored no longer than 48 hours post irradiation.

Questions for the Committee:

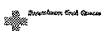
1. Do the committee members agree that the current recommendations regarding the dating period of gamma-irradiated red blood cells should be modified?
2. If so, please comment whether the available scientific data support the following candidate modifications to FDA's current guidance on irradiated red blood cells:
 - a. For red blood cell products that are gamma irradiated within the first 26 days after the date of collection, the products should not be stored more than 28 days from the date of collection.

INFLUENCE OF RADIATION ON RED CELL PROPERTIES

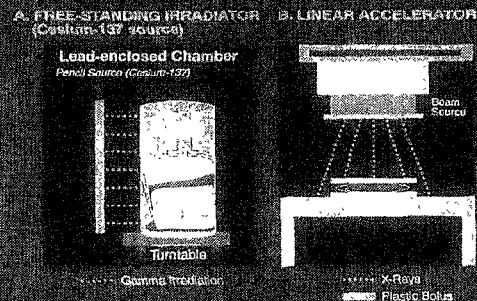
Storage Of Red Cell Units Following Irradiation

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Study Objective

- Evaluation of the influence of gamma radiation dose (2500 cGy) deemed "optimal" for inactivating T-cells in red cell units on red cell properties with different scenarios for time of irradiation/total storage time (days).

Gamma Irradiation – The Basics

- T-cells in red cell units can cause transfusion-associated GVHD.
- Literature notes that transfusion-associated GVHD is fatal in 90% of cases.
- Gamma radiation (x-ray radiation) inactivates T-cells in red cell units (and platelet units).
- Up to the early 1990's, the optimal dose had not been identified in appropriate studies with red cell units.
- Studies conducted with Drs. Luban and Quinones, Children's Hospital, Washington D.C. identified 2500 cGy as the "optimal" dose.

Topics

- Background information on use of a gamma radiation dose of 2500 cGy.
- Influence of radiation on red cell properties.
 - Data from previous studies at the time of the American Red Cross study (period: mid 1990's).
 - American Red Cross Study: Data on in vivo 24 hour red cell recovery and long term survival.
 - American Red Cross Study: Data on in vitro parameters (ATP, hemolysis, extracellular potassium).

Gamma Irradiation versus Leukocyte Reduction

- The dogma is that irradiation is needed to prevent GVHD even when red cell units are leukoreduced.
- The use of leukocyte-reduction as an alternative method has not been documented. Data on the log reduction needed is not known.

Assessment Of Optimal Dose Of Radiation

Comments on Methods

1. A sensitive limiting dilution assay was used in studies in the early 1990's.
2. Assay based on growth of T-cells.
3. Assay measures up to approximately 5 logs of T-cell inactivation.

References:

Pelszynski, Moreff, Luban, Taylor, Quinones - Blood 1994;83:1683-1688

Dose Delivered to Center of Container vs. Center of Canister/Field

1. Studies documenting 2500 cGy as the appropriate dose measured delivery at the center of simulated blood units. [TLD dosimeter chips were placed within blood bags containing water.]
2. Commercial systems for dose mapping measure the delivered dose at the center of the canister (free-standing irradiators).
3. With small 1-unit irradiators, there is essentially no translation issue.
4. With multiple-unit irradiators, there is a translation issue. With 2500 cGy delivered to the canister center point, some units will have a greater dose delivered to their center point.

Evaluation Of Radiation Dose On T-Cell Growth (Summary)

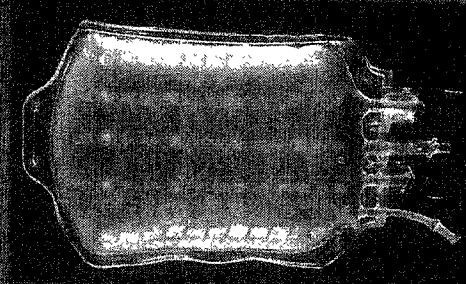
| <u>Dose (cGy)</u> | <u>Growth of T-cells</u> |
|-------------------|--------------------------|
| 500 | Substantial |
| 1000 | Substantial |
| 1500 | Substantial |
| 2000 | Minimal Growth |
| 2500 | No Growth |
| 3000 | No Growth |

Comments:

1. Similar results with radiation delivered to red cells in two Baxter red cell containers (PL2209; PL145)

2. Reference:

Pelszynski, Moreff, Luban, Taylor, Quinones - Blood 1994;83:1683-1688

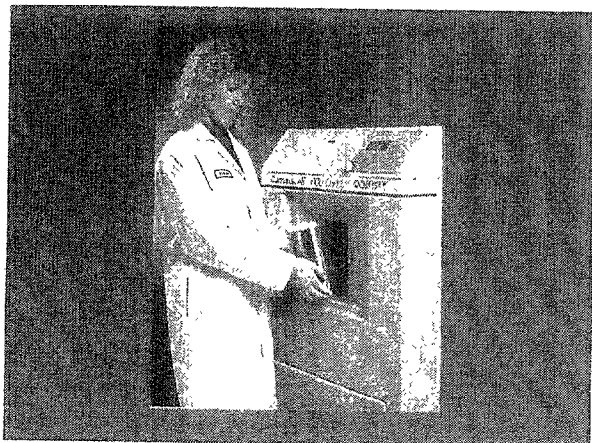


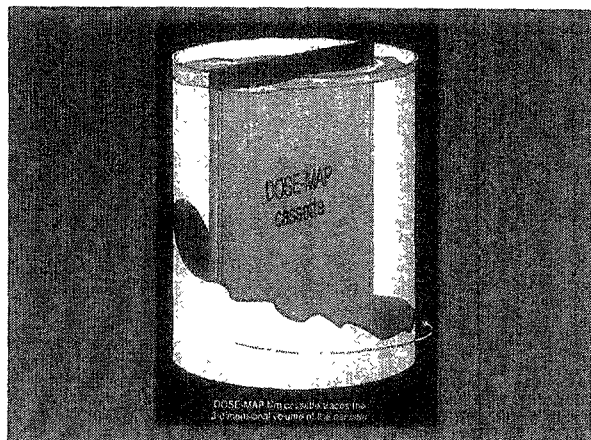
Nomenclature

1 Gy = 100 cGy

1 cGy = 1 rad

2500 cGy = 2500 rad





Methods(1)

- 4 scenarios utilized with radiation treatment on day 1, day 14(2), and day 26 of storage.
- Protocols 1 and 2: two sites.
- Protocols 3 and 4: one site.
- Each subject donated two CPD whole blood units at least 56 days apart. Red cells prepared with AS-1 (ADSOL) preservative solution.
 - On one occasion, AS-1 red blood cells irradiated/stored.
 - On the other occasion, AS-1 red blood cells stored with no irradiation (control).
- Red cell stored in PL 2209 containers (Baxter).
 - No evidence container influences effects of radiation.

Study Objective

- Evaluation of the influence of the gamma radiation dose (2500 cGy) deemed "optimal" for inactivating T-cells in red cell units on red cell properties with different scenarios for time of irradiation/total storage time (days).
 - A paired study approach was used to compare red cell properties with radiation/without radiation.
 - Emphasis on evaluation of in vivo red cell viability properties.

Methods (2)

- Dose of radiation was 2500 cGy – delivered to the mid-section of the blood bag.
- Red cell units were not leukocyte-reduced.

Study Background

- Studies conducted in the mid 1990's.
- Studies sponsored/coordinated by the American Red Cross, Holland Laboratory.
- Principal Site Investigators:
 - James AuBuchon, M.D. – Dartmouth Hitchcock Medical Center, Lebanon, NH.
 - Stein Holme, PhD – American Red Cross, Mid-Atlantic Region, Norfolk, VA.
- Data helped to establish guidelines for irradiation of red cell units.

Previous Reports

Davey R.J., et al (*Transfusion* 32, 525, 1992, NIH Study)

AS-1 Red Cells (Day 0 Irradiation, 3000 cGy)

| Storage Time | 24-Hour Red Cell Recovery | |
|--------------|---------------------------|---------------------|
| | Control | Irradiated |
| 42 days | 78.4 (±7.1) | 68.5 (±8.1) (n = 8) |

Friedman, K.D., et al (*Transfusion* 31, 505, 1991, Univ of Mexico Study)

AS-3 Red Cells (Day 1 Irradiation, 2000 cGy)

| Storage Time | 24-Hour Red Cell Recovery | |
|--------------|---------------------------|---------------|
| | Control | Irradiated |
| 21 days | 90.4% | 82.7% (n = 6) |
| 28 days | 85.0% | 80.7% (n = 6) |

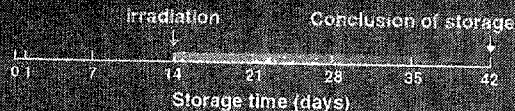
Previous Report: Influence Of 3000 cGy On In Vivo 24 Hour Recovery

Preliminary Study (AS-1 Red Cells, PL 146)

| Conditions | | Single Label | Double Label |
|---|------|--------------|--------------|
| Day 1 Irradiation - Storage for 35 days | 1. | 73.8 | 74.8 |
| | 2. | 87.7 | 89.2 |
| | 3. | 19.5 | 72.3 |
| | 4. | 81.0 | 82.9 |
| | mean | 78.0 | 79.7 |
| Day 14 Irradiation - Storage for 25 days | 1. | 75.0 | 75.2 |
| | 2. | 82.0 | 87.9 |
| | 3. | 76.5 | 87.4 |
| | 4. | 77.5 | 77.4 |
| | mean | 78.5 | 82.0 |

From: P. C. and Anderson, J. Annals of Clinical Lab Science 23:218-220, 1993

Protocol 2



Time of Irradiation and Length of Post-irradiation Storage Period

Protocol 1



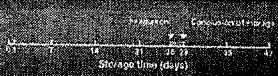
Protocol 2



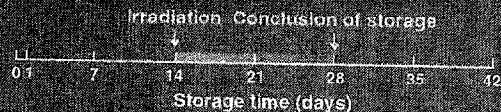
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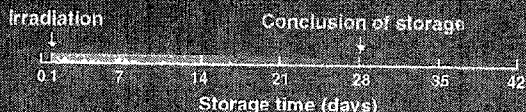
Protocol 4



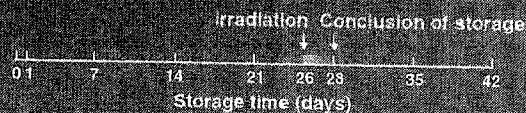
Protocol 3



Protocol 1



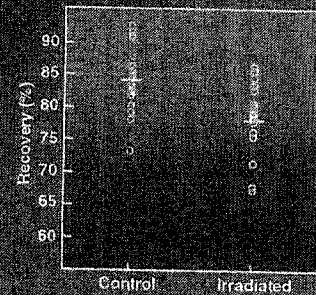
Protocol 4



Methods: 24-Hour In Vivo Red Cell Recovery

- Autologous infusions utilized.
- Data analyzed by the single label method (^{51}Cr) and the double label method (^{51}Cr , ^{99m}Tc).
- Single label – 100% level by back-extrapolation.
- Double label – second label used to determine blood volume and hence 100% ^{51}Cr level.

Individual Unit Data for Control and Irradiated RBCs (n=16) in Protocol 1



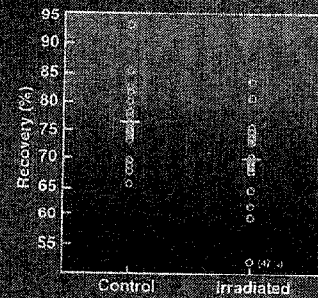
In Vivo 24 Hr Recovery in Control and Irradiated RBCs*

| Day of Irradiation | Time storage (days) | 24 Hr Recovery (%) (Single label) | | | 24 Hr Recovery (%) (Double label) | | | n |
|--------------------|---------------------|-----------------------------------|-----------------|---------|-----------------------------------|-----------------|---------|----|
| | | Control RBCs | Irradiated RBCs | p value | Control RBCs | Irradiated RBCs | p value | |
| 28 | 28 | 85.3 ± 4.5 | 80.3 ± 6.0 | <0.01 | 85.3 ± 4.5 | 80.3 ± 6.0 | <0.01 | 16 |
| 42 | 42 | 78.8 ± 7.4 | 70.8 ± 7.8 | <0.01 | 78.8 ± 7.4 | 70.8 ± 7.8 | <0.01 | 16 |
| 28 | 28 | 83.2 ± 5.7 | 77.0 ± 5.7 | NS | 83.2 ± 5.7 | 77.0 ± 5.7 | NS | 16 |
| 42 | 42 | 84.2 ± 5.1 | 78.6 ± 5.9 | NS | 84.2 ± 5.1 | 78.6 ± 5.9 | NS | 16 |

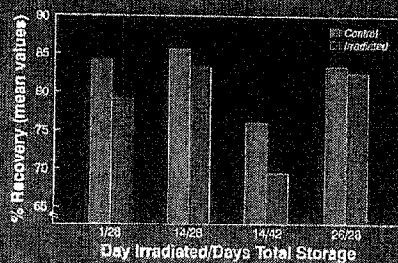
*Values expressed as mean ± SD

Reference: G Moroff, S Hoime, JP AuBuchon, WA Heaton, JD Swannery, LI Friedman: Viability and in vitro properties of AS-1 red cells after gamma irradiation. Transfusion 1999;39:124 – 134.

Individual Unit Data for Control and Irradiated RBCs (n=16) in Protocol 2



24 HOUR IN VIVO RED CELL RECOVERY (%) - SINGLE LABEL



Legend: Control, Irradiated

24-hour Red Cell Recovery (%)

Protocol 1 (Storage – 28 days)

| | Control | Irradiated | p Significance |
|----------|------------|------------|----------------|
| Site A | 85.3 ± 4.5 | 80.3 ± 6.0 | n=8, p<0.01 |
| Site B | 83.2 ± 5.7 | 77.0 ± 5.7 | n=8, p<0.03 |
| Combined | 84.2 ± 5.1 | 78.6 ± 5.9 | n=16, p<0.01 |

Protocol 2 (Storage – 42 days)

| | Control | Irradiated | p Significance |
|----------|------------|------------|----------------|
| Site A | 78.8 ± 7.4 | 70.8 ± 7.8 | n=8, p<0.01 |
| Site B | 73.8 ± 6.1 | 68.1 ± 9.6 | n=8, p<0.05 |
| Combined | 76.3 ± 7.0 | 69.5 ± 8.6 | n=16, p<0.01 |

Influence of Gamma Irradiation on 24-hour In Vivo Red Cell Recovery (%)

| Study | Storage (days) | Irradiation on Day 0/Day 1 | | Comments |
|-------|----------------|----------------------------|------------|-------------------------------|
| | | Control | Irradiated | |
| | 28 | 90.4% | | 2000 cGy, red Paired, NS |
| | 28 | 85.0% | | 2000 cGy, red Paired, AS-1 |
| | 28 | 44.2 ± 6.1% | | 1000 cGy, red Paired, AS-1 |
| | 28 | 81.8 ± 4.4% | | 1000 cGy, red Paired, AS-1 |
| | 28 | 78.4 ± 7.1% | | 1000 cGy, red Paired, AS-1 |

Long-term Survival of RBCs Circulating 24 hours After Transfusion*

| Day of Irradiation | Total storage time (days) | T _{1/2} (days)** | | p value | Number |
|--------------------|---------------------------|---------------------------|-----------------|---------|--------|
| | | Control RBCs | Irradiated RBCs | | |
| | 28 | 28.0 ± 3.3 | | NS | 16 |
| | 42 | 26.4 ± 2.9 | | NS | 16 |
| | 28 | 26.3 ± 2.8 | | NS | 7 |
| | 28 | 27.8 ± 0.6 | | NS | 5 |

* Values expressed as mean ± SD

** Not corrected for elution; calculated with Dornhorst equation

Influence of Gamma Irradiation on 24-hour In Vivo Red Cell Recovery (%)

| Study | Storage (days) | Mid-storage irradiation (on Day 14) | | Comments |
|--------------------|----------------|-------------------------------------|-------------|--------------------------------|
| | | Control | Irradiated | |
| American Red Cross | 42 | 76.3 ± 7.0% | 59.5 ± 8.6% | 2500 cGy, n=16 Paired, AS-1 |
| American Red Cross | 28 | 85.2 ± 2.8% | 82.3 ± 5.0% | 2500 cGy, n=8 Paired, AS-1 |

ATP Levels at the Conclusion of Storage*

| Day of Irradiation | Total storage time (days) | ATP levels (μmol/g hb) | | p value | Number |
|--------------------|---------------------------|------------------------|-----------------|---------|--------|
| | | Control RBCs | Irradiated RBCs | | |
| | 28 | 3.3 ± 0.8 | | NS | 16 |
| | 42 | 2.7 ± 0.7 | | <0.01 | 16 |
| | 28 | 3.7 ± 0.7 | | <0.01 | 5 |
| | 28 | 3.6 ± 0.8 | | NS | 5 |

* Values expressed as mean ± SD

Long-Term Survival

- The long-term survival of RBCs that were circulating 24 hours after infusion was measured in terms of the time at which the circulating ⁵¹Cr was reduced to 50% [T_{1/2} (days)].
- Data analyzed with the Dornhorst model of red cell removal from the circulation.
- Circulating ⁵¹Cr levels were determined in samples obtained 7, 21, 28, and 35 days after the labeled red cells were returned to each subject.
- No correction for elution for ⁵¹Cr; therefore survival time 25-30 days.

Hemolysis Levels at the Conclusion of Storage*

| Day of Irradiation | Total storage time (days) | Hemolysis (%) | | p value | Number |
|--------------------|---------------------------|---------------|-----------------|---------|--------|
| | | Control RBCs | Irradiated RBCs | | |
| | 28 | 0.3 ± 0.1 | | <0.01 | 16 |
| | 42 | 0.8 ± 0.3 | | <0.05 | 16 |
| | 28 | 0.2 ± 0.1 | | NS | 8 |
| | 28 | 0.2 ± 0.1 | | <0.05 | 8 |

* Values expressed as mean ± SD

Influence of Gamma Irradiation on Hemolysis

Irradiation on Day 0/Day 1

| Study | Storage (days) | Mean \pm S.D. Hemolysis* | | Comments |
|--------------------------|----------------|----------------------------|---------------------|---------------------------------|
| | | Control | Irradiated | |
| University of New Mexico | 28 | 0.16% | 0.22% | 2000 cGy, n=6 Paired, AS-3 |
| American Red Cross | 28 | 0.8 \pm 0.1% | 0.8 \pm 0.1% | 2500 cGy, n=6 Paired, AS-1 |
| University of Virginia | 36 | 0.5 \pm 0.1% | 0.6 \pm 0.1% | 3000 cGy, n=4 Unpaired, AS-1 |
| NIH | 42 | 429 \pm 194 mg/dL | 623 \pm 206 mg/dL | 3000 cGy, n=8 Paired, AS-1 |

Conclusions

- Irradiation reduced the retention of red cell properties during storage including 24-hour in vivo recovery; the extent of change depended on storage times post-irradiation.
- For the protocols utilized in the American Red Cross Study, the magnitude of the difference in the 24-hour red cell recovery between control and irradiated units was limited.
- The long term survival parameter was comparable for control and irradiated red cells.

Supernatant Potassium Levels at the Conclusion of Storage*

| Day of Irradiation | Total Storage Time (days) | Potassium (mEq/L) | | P Value | Number |
|--------------------|---------------------------|-------------------|-----------------|---------|--------|
| | | Control RBCs | Irradiated RBCs | | |
| | 36 | 44.9 \pm 6.2 | | <0.01 | 16 |
| | 42 | 62.8 \pm 7.8 | | <0.01 | 18 |
| | 36 | 45.8 \pm 4.2 | | <0.01 | 8 |
| | 28 | 48.2 \pm 3.3 | | <0.01 | 6 |

*Values expressed as mean \pm S.D.

Influence of Gamma Irradiation on Extracellular K⁺

Irradiation on Day 0/Day 1

| Study | Storage (days) | Mean \pm S.D. K ⁺ (mEq/L) | | Comments |
|--------------------------|----------------|--|----------------|---------------------------------|
| | | Control | Irradiated | |
| University of New Mexico | 28 | 47.7 | 46.8 | 2000 cGy, n=6 Paired, AS-3 |
| American Red Cross | 28 | 44.9 \pm 5.3 | 72.3 \pm 6.1 | 2500 cGy, n=6 Paired, AS-1 |
| University of Virginia | 36 | 50 \pm 4.6 | 66 \pm 3.9 | 3000 cGy, n=4 Unpaired, AS-1 |
| NIH | 42 | 42.5 \pm 8.6 | 76.1 \pm 4.4 | 3000 cGy, n=8 Paired, AS-1 |

UNPAIRED RED CELLS - EXTRACELLULAR K⁺ - 4.06%

Evaluation of Gamma Irradiated Red Blood Cells Collected with the Trima Apheresis System

Blood Products Advisory Committee
July 22, 2004

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Acknowledgments

American Red Cross

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Principal Investigator: James P. AuBuchon, MD
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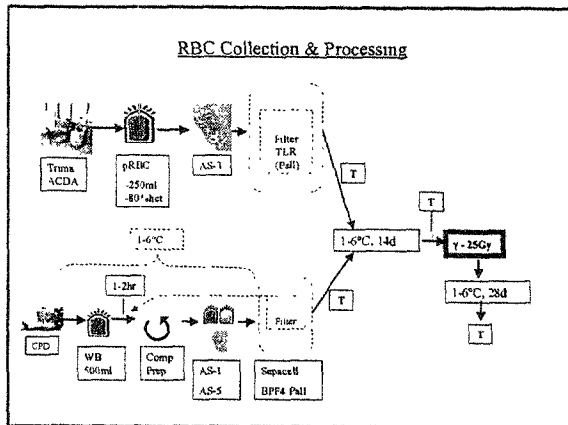
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Objective

Determine the *in vitro* and *in vivo* characteristics of gamma irradiated, apheresis RBC compared to concurrent controls prepared from whole blood



Testing

| | Day 0 | Day 14 | Day 42 |
|--|-------|--------|--------|
| 1 CBC | ✓ | ✓ | ✓ |
| 2 Residual WBC | ✓ | | |
| 3 pH, pO ₂ , pCO ₂ | ✓ | ✓ | ✓ |
| 4 Hb(plasma) → hemolysis | ✓ | ✓ | ✓ |
| 5 ATP | ✓ | ✓ | ✓ |
| 6 Na ⁺ | ✓ | ✓ | ✓ |
| 7 K ⁺ | ✓ | ✓ | ✓ |
| 8. Glucose | ✓ | ✓ | ✓ |
| 9 Osmotic Fragility | ✓ | ✓ | ✓ |
| 10 Radiolabeled Recovery | | | ✓ |

Methods

Gamma Irradiation -
 2500 cGy (1500 cGy minimum) IBL 437C

Radiolabeled RBC *in vivo* recoveries -
 ARC-N : ⁵¹Cr / ^{99m}Tc
 (Heaton et al Vox Sang 1989,57 37-42)
 BCSEW : ⁵¹Cr
 (Moroff et al Transfusion 1984,24 109-114)

Methods

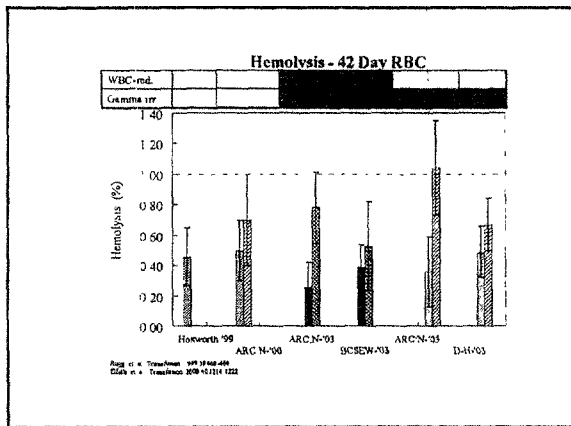
1. **Non-Leukocyte-reduced RBC**
 - a. 2 Centers (D-H, ARC-N)
 - b. Unpaired, parallel group
 - c. 12 subjects per arm per center (48 total)
2. **Leukocyte-reduced RBC**
 - a. 2 Center (ARC-N, BCSEW)
 - b. Randomized, Paired, Crossover
 - c. 12 subjects per center

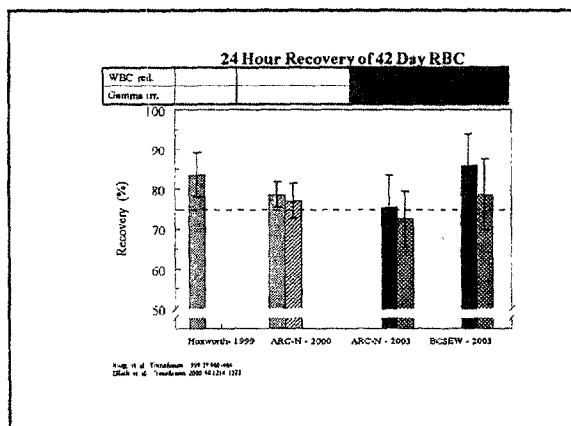
Unpaired, Non-Leukocyte-reduced RBC - (mean \pm sd)
N=12 Trima, N=12 WB at each center WB: Teruma, AS-5
Gamma irradiation after Day 14 sample

| | K ⁺ (mM) | | ATP (μ mol/g Hb) | | Hemolysis (%) | |
|--------|---------------------|----------------|-----------------------|-----------------|-----------------|-----------------|
| | WB | Trima | WB | Trima | WB | Trima |
| D-H | | | | | | |
| Day 14 | 39.7 \pm 6.4 | 28.9 \pm 3.9 | 4.2 \pm 1.6 | 4.0 \pm 0.9 | 0.13 \pm 0.03 | 0.12 \pm 0.03 |
| | | p=0.0001 | | p=0.46 | | p=0.6 |
| Day 42 | 77.1 \pm 2.4 | 72.9 \pm 6 | 2.6 \pm 1.1 | 2.6 \pm 0.83 | 0.67 \pm 0.17 | 0.49 \pm 0.44 |
| | | p=0.026 | | p=0.85 | | p=0.17 |
| ARC-N | | | | | | |
| Day 14 | 35.1 \pm 5.7 | 24.3 \pm 2.7 | 4.7 \pm 0.61 | 4.5 \pm 0.73 | 0.15 \pm 0.08 | 0.09 \pm 0.02 |
| | | p=0.0001 | | p=0.5 | | p=0.011 |
| Day 42 | 67.1 \pm 2.0 | 59.2 \pm 2.6 | 2.37 \pm 0.52 | 2.13 \pm 0.62 | 1.04 \pm 0.31 | 0.36 \pm 0.23 |
| | | p=0.0001 | | p=0.3 | | p=0.0001 |

Paired Leukocyte-reduced RBC - (mean \pm sd) n=12 pairs at each center
Gamma irradiation after Day 14 sample

| | K ⁺ (mM) | | ATP (μ mol/g Hb) | | Hemolysis (%) | | 24 hr. Recovery (%) | |
|---------------------------|---------------------|----------------|-----------------------|---------------|-----------------|-----------------|---------------------|----------------|
| | WB | Trima | WB | Trima | WB | Trima | WB | Trima |
| ARC-N (AS5, BPF4) | | | | | | | | |
| Day 14 | 34.7 \pm 6.2 | 24.8 \pm 2.3 | 4.3 \pm 0.7 | 4.8 \pm 0.7 | 0.18 \pm 0.07 | 0.18 \pm 0.11 | | |
| | | p=0.0005 | | p=0.025 | | p=0.9 | | |
| Day 42 | 67.1 \pm 2.0 | 61.8 \pm 2.3 | 2.3 \pm 0.6 | 2.5 \pm 0.5 | 0.78 \pm 0.23 | 0.26 \pm 0.14 | 72.5 \pm 7.0 | 75.6 \pm 7.7 |
| | | p=0.0004 | | p=0.17 | | p=0.0001 | | p=0.078 |
| BCSEW (AS1, RS2000) | | | | | | | | |
| Day 14 | 26.8 \pm 4.4 | 25.4 \pm 2.3 | 5.1 \pm 0.6 | 5.2 \pm 0.7 | 0.10 \pm 0.02 | 0.16 \pm 0.06 | | |
| | | p=0.3 | | p=0.47 | | p=0.003 | | |
| Day 42 | 64.8 \pm 7.7 | 67.0 \pm 2.4 | 2.9 \pm 0.7 | 2.9 \pm 0.5 | 0.53 \pm 0.29 | 0.39 \pm 0.15 | 78.6 \pm 8.9 | 85.9 \pm 8.0 |
| | | p=0.127 | | p=0.8 | | p=0.064 | | p=0.014 |





Conclusions

1. 42 day Apheresis RBC collected by Trima,
 - stored in ACD-A/AS-3,
 - gamma irradiated on day 14 of storage
 are not inferior to –

Control RBC from whole blood
stored and irradiated in a similar manner
2. Average 24 hour *in vivo* recoveries for Trima RBC > 75%

**Statement of
The American Association of Blood Banks
Before the Blood Products Advisory Committee**

July 22, 2004

Dating of Irradiated Blood Products

**Presented by M. Allene Carr-Greer, MT(ASCP)SBB
Deputy Director, Regulatory Affairs**

AABB is an international association dedicated to advancing transfusion and cellular therapies worldwide. Our members include more than 1,800 hospital and community blood centers and transfusion and transplantation services as well as approximately 8,000 individuals involved in activities related to transfusion, cellular therapies and transplantation medicine. For over 50 years, AABB has established voluntary standards for, and accredited institutions involved in, these activities. AABB is focused on improving health through the advancement of science and the practice of transfusion medicine and related biological therapies, developing and delivering programs and services to optimize patient and donor care and safety.

BPAC previously discussed the issue of irradiation of blood products collected in novel anticoagulants/additive solutions at the March 2003 advisory committee meeting. These novel solutions are used with automated collection systems and have not been specifically approved for use in red blood cells (RBCs) that are to be irradiated (or frozen and deglycerolized). At that time, FDA explained the rationale used in deciding to permit the affected blood components to continue to be irradiated and distributed for transfusion. During the open public hearing, it was brought to the attention of the committee that once the product has been irradiated and stored for a period of time, there may be issues of concern related to the 24-hour percent recovery of RBCs. This was a potential concern for irradiated products collected both manually and by automated methods.

The AABB appreciates that FDA permitted the continued use of blood products collected in novel solutions pending review of the sponsor studies on RBCs collected and stored in anticoagulant/preservative solutions approved for their devices.

Beginning with the 9th edition (1978) of "Standards for Blood Banks and Transfusion Services," AABB has included language regarding irradiation of blood or blood components, and anticoagulants/additive solutions are not discussed. Memoranda and guidance documents issued by FDA have never mentioned restrictions on irradiation with regard to anticoagulants/additive solutions.

As FDA considers changes to current guidelines for the irradiation of blood and blood components, AABB encourages the agency to base its decisions on sound scientific data, and to be mindful of the effects of these changes on transfusion services and blood collection facilities. Computer programs are integral to component creation, processing, and assignment of outdate, and these programs must be re-validated when modifications occur. Subsequent to that, changes to Standard Operating Procedures and training of affected staff will be necessary. In particular, AABB requests that if FDA proposes any changes to the expiration date of irradiated products, the guidance documents specifically address issues related to irradiation of blood donations from family members and other instances of medical need that may fall outside the new proposals.