

Blood component & substitute therapies in ICU

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- Need for grouping
- Anti coagulation
- Preservation

From World War I to 1990's

- Infections
 - Hepatitis
 - HIV
- Reconsider indications
- Switching to component Rx
- Recombinant factors
- Substitute therapies

Anemia in ICU

- Very common, ~ 95% of patient's Hb < normal by day 3
- >50% of pts receive RBC transfusions during their ICU stay
- > 85% for those staying > 1 week
- ~ 14 % medical & 25 % surgical pts receive transfusions everyday in ICU

Etiology

- Ongoing blood loss
- Hemolysis
- Phlebotomy
- Anemia of critical illness
 - Low serum iron, TIBC, high ferritin
 - Low endogenous erythropoietin
 - Poor response to same

Management of anemia

- Anemia was synchronous with poor O₂ delivery & tissue hypo perfusion
- Maintaining high Hb was thought to improve mortality
- Since 1942, rule of 10 / 30 was followed with no RCTs to back up the argument
- Few small retrospective & prospective trials looked at evidence in the 90's

Review of the clinical practice literature on allogeneic red blood cell transfusion

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Retrospective studies - unnecessary transfusions ~ 4-60 %

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Results Overall, 30-day mortality was similar in the two groups (18.7 percent vs. 23.3 percent, $P=0.11$). However, the rates were significantly lower with the restrictive transfusion strategy among patients who were less acutely ill — those with an Acute Physiology and Chronic Health Evaluation II score of ≤ 20 (8.7 percent in the restrictive-strategy group and 16.1 percent in the liberal-strategy group, $P=0.03$) — and among patients who were less than 55 years of age (5.7 percent and 13.0 percent, respectively; $P=0.02$), but not among patients with clinically significant cardiac disease (20.5 percent and 22.9 percent, respectively; $P=0.69$). The mortality rate during hospitalization was significantly lower in the restrictive-strategy group (22.2 percent vs. 28.1 percent, $P=0.05$).

TABLE 2. OUTCOMES.*

OUTCOME MEASURE	RESTRICTIVE- TRANSFUSION STRATEGY (N= 418)	LIBERAL- TRANSFUSION STRATEGY (N= 420)	ABSOLUTE DIFFERENCE BETWEEN GROUPS	95% CONFIDENCE INTERVAL	P VALUE
				percent	
Death — no. (%)					
30-day	78 (18.7)	98 (23.3)	4.7	−0.84 to 10.2	0.11
60-day†	95 (22.7)	111 (26.5)	3.7	−2.1 to 9.5	0.23
ICU	56 (13.4)	68 (16.2)	2.3	−2.0 to 7.6	0.29
Hospital	93 (22.2)	118 (28.1)	5.8	−0.3 to 11.7	0.05
Multiple-organ-dysfunction score					
Unadjusted score	8.3±4.6	8.8±4.4	0.5	−0.1 to 1.1	0.10
Adjusted score‡	10.7±7.5	11.8±7.7	1.1	0.8 to 2.2	0.03
Change from base-line score§	3.2±7.0	4.2±7.4	1.0	0.1 to 2.0	0.04
No. of organs failing — no. (%)					
0	100 (23.9)	82 (19.5)			
1	136 (32.5)	149 (35.5)			
2	109 (26.1)	108 (26.0)			
3	51 (12.2)	63 (15.0)			
>3	22 (5.3)	18 (4.3)	1.8¶	−3.4 to 7.1¶	0.53¶
Length of stay — days					
ICU	11.0±10.7	11.5±11.3	0.5	−1.0 to 2.1	0.53
Hospital	34.8±19.5	35.5±19.4	0.7	−1.9 to 3.4	0.58

(N Engl J Med 1999;340:409-17.)

TABLE 3. COMPLICATIONS THAT OCCURRED DURING THE PATIENTS' STAYS IN THE INTENSIVE CARE UNIT.

COMPLICATION*	RESTRICTIVE- TRANSFUSION STRATEGY (N=418)	LIBERAL- TRANSFUSION STRATEGY (N=420)	ABSOLUTE DIFFERENCE BETWEEN GROUPS	95% CONFIDENCE INTERVAL†	P VALUE
	no. (%)		percent		
Cardiac	55 (13.2)	88 (21.0)	7.8	2.7 to 12.9	<0.01
Myocardial infarction	3 (0.7)	12 (2.9)	2.1	—	0.02
Pulmonary edema	22 (5.3)	45 (10.7)	5.5	1.8 to 9.1	<0.01
Angina	5 (1.2)	9 (2.1)	0.9	—	0.28
Cardiac arrest	29 (6.9)	33 (7.9)	0.9	-2.6 to 4.5	0.60
Pulmonary	106 (25.4)	122 (29.0)	3.7	-2.3 to 9.7	0.22
ARDS	32 (7.7)	48 (11.4)	3.8	-0.2 to 7.8	0.06
Pneumonia	87 (20.8)	86 (20.5)	-0.3	-5.8 to 5.1	0.92
Infectious	42 (10.0)	50 (11.9)	1.9	-2.4 to 6.1	0.38
Bacteremia	30 (7.2)	40 (9.5)	2.3	-1.4 to 6.1	0.22
Catheter-related sepsis	21 (5.0)	17 (4.0)	-1.0	-3.8 to 1.8	0.50
Septic shock	41 (9.8)	29 (6.9)	-2.9	-6.7 to 0.8	0.13
Hematologic‡	10 (2.4)	10 (2.4)	0	-2.1 to 2.1	1.00
Gastrointestinal§	13 (3.1)	19 (4.5)	1.4	-1.2 to 4.0	0.28
Neurologic¶	25 (6.0)	33 (7.9)	1.9	-1.6 to 5.3	0.28
Shock	67 (16.0)	55 (13.1)	-2.9	-7.7 to 1.8	0.23
Any complication	205 (49.0)	228 (54.3)	5.2	-1.5 to 12.0	0.12

(N Engl J Med 1999;340:409-17.)

The CRIT Study: Anemia and blood transfusion in the critically ill—Current clinical practice in the United States*

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Objective: To quantify the incidence of anemia and red blood cell (RBC) transfusion practice in critically ill patients and to examine the relationship of anemia and RBC transfusion to clinical outcomes.

Design: Prospective, multiple center, observational cohort study of intensive care unit (ICU) patients in the United States. Enrollment period was from August 2000 to April 2001. Patients were enrolled within 48 hrs of ICU admission. Patient follow-up was for 30 days, hospital discharge, or death, whichever occurred first.

Setting: A total of 284 ICUs (medical, surgical, or medical-surgical) in 213 hospitals participated in the study.

Patients: A total of 4,892 patients were enrolled in the study.

Measurements and Main Results: The mean hemoglobin level at baseline was 11.0 ± 2.4 g/dL. Hemoglobin level decreased throughout the duration of the study. Overall, 44% of patients received one or more RBC units while in the ICU (mean, 4.6 ± 4.9 units). The mean pretransfusion hemoglobin was 8.6 ± 1.7 g/dL. The mean time to first ICU transfusion was 2.3 ± 3.7 days. More

RBC transfusions were given in study week 1; however, in subsequent weeks, subjects received one to two RBC units per week while in the ICU. The number of RBC transfusions a patient received during the study was independently associated with longer ICU and hospital lengths of stay and an increase in mortality. Patients who received transfusions also had more total complications and were more likely to experience a complication. Baseline hemoglobin was related to the number of RBC transfusions, but it was not an independent predictor of length of stay or mortality. However, a nadir hemoglobin level of <9 g/dL was a predictor of increased mortality and length of stay.

Conclusions: Anemia is common in the critically ill and results in a large number of RBC transfusions. Transfusion practice has changed little during the past decade. The number of RBC units transfused is an independent predictor of worse clinical outcome. (Crit Care Med 2004; 32:39–52)

KEY WORDS: anemia; blood transfusion; transfusion practice; transfusion risks

- Jacques Lacroix et al in a recently published study in NEJM showed a restrictive transfusion strategy in PICU with target Hb of > 7 gm/dl is a/w no worse outcome even in pediatric population

Experience in our RICU

- Majority of transfusions – restrictive strategy
 - Significant deviation in FFP & plt transfusions
- Transfused pts
 - Significantly worse outcome
 - Prolonged ventilation, ICU & hospital stay
 - Increased incidence of nosocomial infections

Heart disease & transfusion

- Studies in pts undergoing CABG have shown consistent worse outcome in the presence of anemia
- TRICC failed to show in sub group analysis superiority of liberal transfusion over restrictive strategy in stable IHD
- Till results of “FOCUS trial” are available, it would be prudent to maintain Hb > 9 gm/dl in the presence of heart disease

Why liberal transfusion is counterproductive ?

- Exact reason is unclear
- Proposed mechanisms include
 - Storage lesion effect
 - TRIM (transfusion related immunomodulation)

Storage lesion effect

- Biochemical & biomechanical changes in the RBC and storage media during preservation that reduce RBC survival & function
- Storage of up to 35 to 42 days is possible by the addition of phosphate, adenine, and nutrient solutions
- RBC survival = % radio labeled in periphery at 24 hrs post transfusion
- Traditionally > 70% was thought to be adequate

Duration of Red-Cell Storage and Complications after Cardiac Surgery

METHODS

We examined data from patients given red-cell transfusions during coronary-artery bypass grafting, heart-valve surgery, or both between June 30, 1998, and January 30, 2006. A total of 2872 patients received 8802 units of blood that had been stored for 14 days or less (“newer blood”), and 3130 patients received 10,782 units of blood that had been stored for more than 14 days (“older blood”). Multivariable logistic regression with propensity-score methods was used to examine the effect of the duration of storage on outcomes. Survival was estimated by the Kaplan–Meier method and Blackstone’s decomposition method.

RESULTS

The median duration of storage was 11 days for newer blood and 20 days for older blood. Patients who were given older units had higher rates of in-hospital mortality (2.8% vs. 1.7%, $P=0.004$), intubation beyond 72 hours (9.7% vs. 5.6%, $P<0.001$), renal failure (2.7% vs. 1.6%, $P=0.003$), and sepsis or septicemia (4.0% vs. 2.8%, $P=0.01$). A composite of complications was more common in patients given older blood (25.9% vs. 22.4%, $P=0.001$). Similarly, older blood was associated with an increase in the risk-adjusted rate of the composite outcome ($P=0.03$). At 1 year, mortality was significantly less in patients given newer blood (7.4% vs. 11.0%, $P<0.001$).

CONCLUSIONS

In patients undergoing cardiac surgery, transfusion of red cells that had been stored for more than 2 weeks was associated with a significantly increased risk of postoperative complications as well as reduced short-term and long-term survival.

TRIM

- Decreased helper T-cell count
- Decreased helper/suppressor T-lymphocyte ratio
- Decreased lymphocyte response to mitogens
- Decreased natural killer (NK) cell function
- Reduction in delayed-type hypersensitivity
- Defective antigen presentation
- Suppression of lymphocyte blastogenesis
- Decreased cytokine (IL-2, interferon- γ) production
- Decreased monocyte/macrophage phagocytic function

Immunosuppression Or Alloimmunization

Other complications

- Acute hemolytic transfusion reaction
 - Incompatible transfusion
 - Clerical error
 - Rare (1 : 77,000)
- Delayed hemolytic transfusion reactions
 - Prior sensitization to antigen
 - Previous transfusion or pregnancy
 - Delayed hemolysis (5-10 days after)
 - Usually not severe

- Febrile nonhemolytic transfusion reaction
 - 1 degree C rise in temp within 1 hour of completion of transfusion
 - Sensitization to antigens on donor leukocytes
 - Very common with plt transfusions & in pts receiving multiple transfusions
 - Prevented by leukoreduction
 - Treated with antipyretics, steroids & anti histamines
- Infections
- TRALI

TRALI

- Occurs in 1: 5000 to 1:1300 transfusions
- Most common cause of transfusion related mortality in USA
- Mortality ~ 5 – 25 %
- Can occur with as less as 1-2 ml transfusion
- Most common with plasma based transfusions

Prevention of TRALI

- Restrictive transfusion strategy
- Temporary exclusion of donors implicated in previous episodes of TRALI
- Testing of donors for antibodies to high frequency leucocyte antigens (HNA-3a, HLA-A2 & HLA-B12) disqualification if positive
- Disqualification of multiparous women from plasma donation (UK)

Strategies to decrease transfusion

- Decrease blood loss
 - Sampling loss
 - Antifibrinolytics
 - Desmopressin
 - Activated factor VII
 - Blood recovery techniques
- Increase Hb production
 - Erythropoietin
- Substitute therapy

Reducing blood loss from diagnostic sampling

- Important cause of blood loss
- Studies from the 1980s
 - 377 mL/d in CTVS ICUs, 240 mL/d in surgical & 41.5 mL/d in medical–surgical ICUs
- More recent study ~1136 pts
 - 41.1 mL/d per patient !!!
- May indirectly contribute ~ 50% transfusion indications

Factors dictating sampling

- Severity of illness
- Ease of sampling
 - Presence of central indwelling catheters ensure easier access & more blood withdrawal
 - Need to discard first few ml of blood
- Amount of blood required by lab
- Unnecessary investigations

Antifibrinolytics

- Evaluated to prevent perioperative blood loss
 - Initial meta-analysis of small studies had suggested decrease in transfusions without increase in adverse events
- Large RCT comparing aprotinin vs. lysine analogs – NEJM 2008 (BART study group)
 - Modest reduction in massive bleed
 - Strong & consistent increase in mortality

Recombinant activated factor VII

- Approved for use in specific factor deficiency & plt function defect
- Case series & reports claiming its efficacy in uncontrolled non specific bleed
- Bosch et al evaluated its use blunt trauma abdomen & GI bleed in separate studies and failed to show decreased mortality or transfusions
- Phase II study in ICH showed improved survival & disability
- Subsequent study failed to show similar benefit

Not recommended for routine use outside research setting

Efficacy and Safety of Epoetin Alfa in Critically Ill Patients

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BACKGROUND

Anemia, which is common in the critically ill, is often treated with red-cell transfusions, which are associated with poor clinical outcomes. We hypothesized that therapy with recombinant human erythropoietin (epoetin alfa) might reduce the need for red-cell transfusions.

METHODS

In this prospective, randomized, placebo-controlled trial, we enrolled 1460 medical, surgical, or trauma patients between 48 and 96 hours after admission to the intensive care unit. Epoetin alfa (40,000 U) or placebo was administered weekly, for a maximum of 3 weeks; patients were followed for 140 days. The primary end point was the percentage of patients who received a red-cell transfusion. Secondary end points were the number of red-cell units transfused, mortality, and the change in hemoglobin concentration from baseline.

CONCLUSIONS

The use of epoetin alfa does not reduce the incidence of red-cell transfusion among critically ill patients, but it may reduce mortality in patients with trauma. Treatment with epoetin alfa is associated with an increase in the incidence of thrombotic events. (ClinicalTrials.gov number, NCT00091910.)

Epoetin alfa is expensive, does not decrease mortality or transfusion requirements & may be associated with increased risk of complications

Ideal blood substitute

- Safe
- Oxygen delivery
 - Carrying capacity
 - Ability to deliver(P 50)
- Half life
- Viscosity
- Vasoactivity
- Storage & stability
- Sterility & non immune
- Clearance & metabolism
- Lab issues

Hemoglobin as acellular O₂ carrier

- Logical alternative to RBC
- Four basic problems

Polymerization / conjugation of Hb

- Even small amounts of stromal contamination- highly toxic
- Source
 - Out dated blood (only 5-10% gets outdated)
 - Bovine
 - Recombinant

Perfluorocarbons

- Synthetic compounds made of fluorine atoms replacing hydrogen atoms along an 8-10 molecule carbon backbone
- Highly hydrophobic and lipophobic, and are chemically inert compounds
- Oxygen binding is linear & hence requires PaO₂ of > 300 mm Hg to be effective

Fresh frozen plasma

- Tendency to transfuse FFP to critically ill pts with mild coagulopathy
- Often given prophylactically
- Plasma based blood products are a/w high risk of complications
 - TRALI
 - TACO
 - Allergic reactions
- INR 1.5 – 2 is the usual trigger (even in non bleeders)
- Estimates show ~ 50 % of plasma transfused may be unnecessary

FFP -Dosage for Transfusion

- Volume of 1 unit FFP: 200-250 mL
- 1 mL plasma contains 1 unit coagulation factors
- 1 unit FFP contains 220 unit coagulation factors

Factor recovery with transfusion = 40%

- 1 unit FFP provides ~80 unit coagulation factors
- In a 70 kg Patient
 - 1 unit FFP increases most factors ~2.5%
 - 4 units FFP increase most factors ~10%
- Minimum increase ~ 10% required to make difference in coagulation parameters

Platelet – dosage for transfusion

- One unit of random pooled plts increases count by ~ 7000 in a 70 kg adult
- In absence of antibodies or active consumption
- Usual dose used is ~ 1 unit / 15 kgs
- 1 unit contains ~ 60 ml of plasma, few RBCs & leukocytes
- 4- 6 units – used in prophylactic transfusions
- SDAP ~ 4-6 units of plts from single compatible donor

Conclusion

- Small measures aimed at blood conservation go a long way
- Restrictive strategy
 - Hb 7-9 gm/dl
 - Trigger not to be based on Hb alone
 - In presence of IHD maintain Hb > 9 gm/dl until further studies are available
- Substitute therapies are still experimental
- Use plasma & plts wisely & judiciously