REX

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Transfusions: Do they help or hurt?

Do we really know what transfusions accomplish?

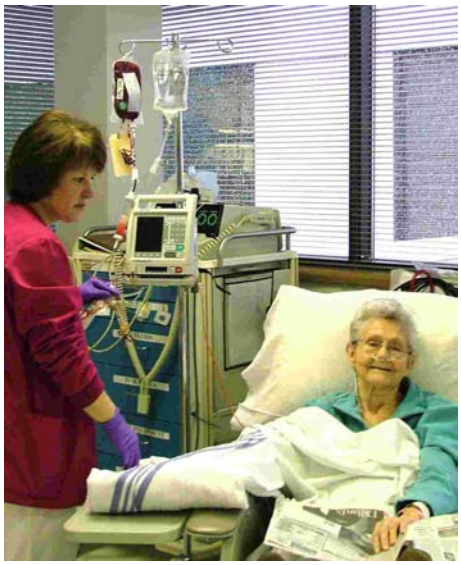
Much of the discussion regarding blood transfusion concentrates on risks including viral infection, recipient misidentification leading to hemolytic transfusion reactions, TRALI (Transfusion Related Acute Lung Injury) or bacterial contamination of blood products. (Table 1) While such discussion and awareness are essential to making good clinical decisions, the physiologic benefits of transfusion deserve careful scrutiny. Do we really know that transfusions are as helpful as many of us assume or were taught in medical training? The more I read about this subject, the more skeptical I become about the actual benefits of blood transfusion. Let me share some fascinating and eye-opening observations that have been nicely summarized in a recent article appearing in the journal Transfusion.

TABLE 1. Risks of transfusion (the classics)*

Risk	Incidence
1. Hepatitis B	1/5,800-1/150,000 units
2. Hepatitis C	1/872,000 units
3. HIV	1/1.4-2.4 million
4. HTLV	1/1.5 million
5. West Nile virus	1/1.4 million
6. Cytomegalovirus conversion	7%
7. Epstein-Barr virus	0.5%
8. TRALI	1/5,000-10,000
9. ABO-Rh mismatch	
Occurrence	1/6,000-20,000
Mortality	1/100,000-500,000
10. Delayed hemolytic reaction	1/2,500
11. Alloimmunization (PLTs and WBCs)	1/10
12. Alloimmunization (RBCs)	1%
13. Allergic reactions	1%-4%
14. Febrile reaction	0.1%-1%
15. GVHD	1/400-1/10,000
16. Volume overload	10%-40%
17. Depressed erythropoiesis	Universal

**Some of the reported risks of transfusion. Data are reported either as risk per number of units transfused or as percentage.*

Red Blood Cell (RBC) transfusions are presumably given to increase oxygen-carrying capacity. However, there is no adequate single clinical or laboratory indicator that can tell you when a transfusion will be required. Despite the fact that transfusion is a widely utilized therapeutic intervention, and most physicians believe it is beneficial in appropriate clinical circumstances, there is very little carefully controlled research telling us when transfusion actually improves patient outcomes. In the early twentieth century, the so-called transfusion trigger was a hemoglobin (Hgb) of about 4 g/dl. Later research showed this is the hemoglobin at which critical oxygen demand (DO_2) is found in anemic humans. In the 1920s, this transfusion trigger rose to 5 - 7 g/dl based on the concept that transfusion should be given prophylactically to avoid the shock and congestive heart failure observed at critical DO_2. Then in 1947, a single influential physician published his opinion that the transfusion trigger for surgery should be 10 g/dl, although this was not based on laboratory research or human outcome studies. This opinion was promulgated through textbooks and physician training programs for decades. When the HIV crisis of the 1980s emerged, the transfusion trigger was once again more critically evaluated and has since decreased once again to the 7 - 9 g/dl range. However, only a few very small prospective studies have examined the risk-to-benefit ratio of transfusion.



Basic red blood cell and end organ physiology explains some recent intriguing observations about transfusion effects. RBCs for transfusion are stored at 40°C in the blood bank for up to 42 days. Stored RBCs undergo a number of physiologic changes. Despite the use of additive solutions to help survival, RBCs undergo anaerobic

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glycolysis to maintain cellular integrity, quickly becoming acidotic. Potassium leaks out of the red cells. With the additive solutions, intracellular adenosine diphosphate is relatively well maintained but the intracellular 2,3-diphosphoglyceratae (2,3-DPG) levels fall rapidly after collection. This causes the Hb in stored cells to avidly bind and hold oxygen. This oxygen affinity continues when initially transfused, and the RBCs do not release oxygen to the tissues. The stored RBCs actually take oxygen from circulating plasma, other normal RBCs, and even from tissue myoglobin. A recent prospective study of oxygen delivery to tissues in patients after cardiac surgery found that the transfusion of one or two units of RBCs did nothing to improve oxygen delivery to striated muscle until a shift to 100 percent O^2 breathing occurred. Therefore, the presumed RBC oxygen-carrying capacity may be doing nothing or worsening the release of oxygen to the tissues that it is targeted to help.

Within five to 24 hours after transfusion, metabolic repair of the cellular dysfunctions begins. Potassium is reabsorbed and 2,3-DPG is replenished. The stored RBCs have lost about 20 - 30% of cell membrane lipid and cytoskeletons become inflexible. Cell-to-cell interactions through fibrin cross-linking lead to microaggregate formations that increase both in number and in the number of cells per microaggregate over the length of storage. Perhaps some of the counterintuitive observations about transfused RBCs make more sense in the context of these storage lesions.

Recent studies have demonstrated that patients transfused either during heart surgery or in critical care units have worse P50 values (the PO2 at which the hemoglobin becomes 50% saturated with oxygen) after transfusion of RBC units. Gastric wall pH as measured by gastric tonometry has shown that patients transfused with RBCs acutely have worsened gut mucosal oxygen supply than before transfusion. In animal models of the microcirculation it has been shown that if hemorrhagic shock is induced the mesenteric blood flow is dramatically decreased. When banked blood is transfused, however, only about ten to 15 percent of mesenteric blood flow is restored, and it is unclear how long after volume restoration mesenteric flow remains depressed. In studies of the microcirculation and oxygen delivery to the tissues in need, it is also clear that these tissues are either not restored to normal oxygen supply demand ratios or are made worse. Several studies of cardiac surgery patients have examined the effect of hemoglobin on outcome, and found a graded increase in mortality, stroke, return to surgery, and other adverse outcomes with lowest Hgb on bypass. However these studies did not look at transfusion as an independent variable in their studies. Therefore, one cannot tell whether adverse outcomes were due to low Hgb alone or the effects of transfusion itself.

Although studies allowing low Hgb to develop in a cohort of patients are difficult to justify (given current dogma), data from Jehovah's Witness patients clearly demonstrate anemia is tolerated quite well. In fact, it is only at a Hgb level of approximately 3 to 5 g/dl that mortality dramatically increases. This level of Hgb corresponds to the critical Hgb level from animal models of critical DO_2, i.e. the point at which metabolism shifts from aerobic to anaerobic. The longer an organism spends below critical DO_2 the more likely organ damage is to occur. Furthermore, studies in animals have shown that when stored animal blood (stored the same way as human banked blood) is transfused the critical DO_2 occurs at an even higher Hgb than without transfusion, meaning that shock is more likely after transfusion.

A study of cardiac surgery patients examined the correlation of low hematocrit (Hct) during bypass to adverse outcome and whether transfusion mitigates those risks. (see Figure 1.) As renal failure after heart surgery is thought to be due to

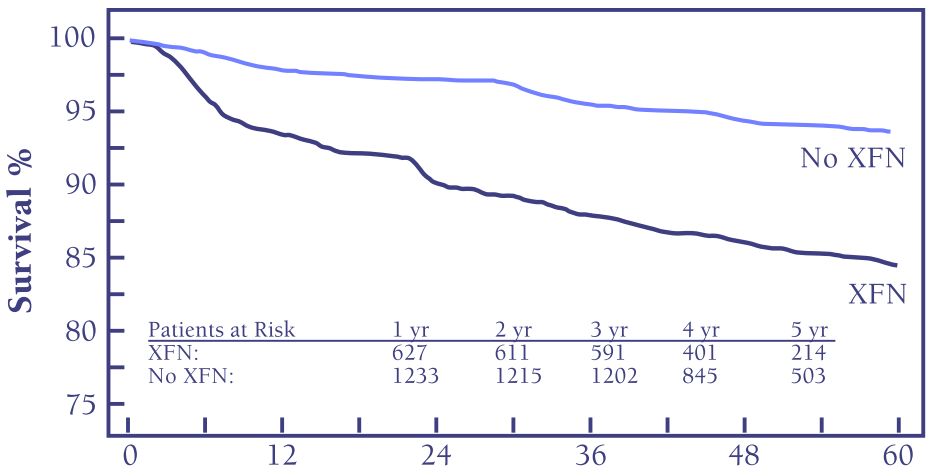

Figure 1. The Kaplan-Meier mortality curves for those cardiac surgery patients transfused perioperatively (XFN) and for those not transfused (No XFN). Those patients not transfused had approximately 2.5-fold better survival than those that received one or more units of RBCs during their CABG hospital stay. These data were after propensity analysis weighting confounding events and risks.

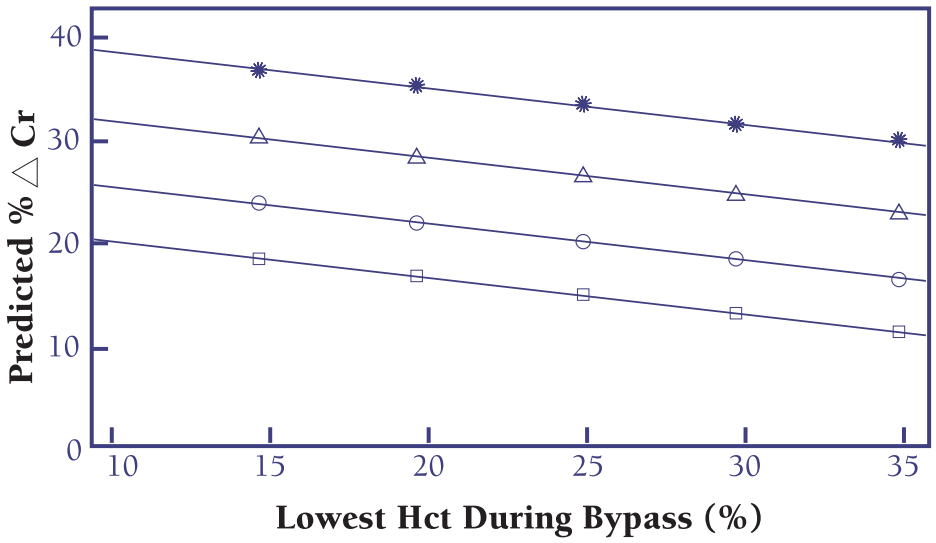

Figure 2. The influence of blood transfusion on the relationship between lowest hematocrit (Hct) during cardiopulmonary bypass and peak postoperative fractional change in creatinine (%△Cr). RBCs: top line (asterisks) = 9; second line (triangles) = 6; third line (circles)=3; fourth line (squares) = 0 RBCs. (RBCs = number of units of packed red blood cells transfused intraoperatively)

hypoperfusion, they studied the correlation between the postoperative rise in creatinine and the lowest Hct during cardiopulmonary bypass. They found such a correlation, but more importantly, transfusion did not change this relationship. With each increased level of transfusion utilization, the amount of creatinine rise worsened. Therefore, transfusion actually worsened renal dysfunction. (see Figure 2) Perhaps the effects of inflammation or the effects of stored blood on microcirculation, microaggregates, and decreased oxygen release all play a role in this finding. A single-center study of transfusion during almost 2000 CABG surgeries found that transfusion had important effects on long-term outcome. Mortality occurred at twice the rate in patients transfused compared to those not transfused. This finding remained true for up to the 60 months of follow-up.

A few prospective randomized studies of transfusion have been performed. One such study examined transfusion for heart surgery with two different levels of transfusion trigger. These triggers showed no difference in outcome in more than 200 patients and the conclusion was that anemia was well tolerated. The largest prospective trial of transfusion to date (838 patients) found significant differences in those transfused at different triggers. This study was a cooperative effort by intensive care units with patients randomized to receive transfusion at either 10 or 7 g/dl.. Many of these patients had known coronary artery disease, adult respiratory distress syndrome, gastrointestinal bleeds, and other critical illnesses. The data showed a trend toward lower mortality overall in this group using a more restrictive transfusion trigger (7 g/dL) but it was significant only at the p level of 0.10. In those patients below age 55 and those with fairly low APACHE scores, however, there was a significant decrease in mortality in those patients transfused less. Overall, hospital mortality was less in those receiving fewer transfusions. Nowhere in the data was outcome better in those patients transfused more liberally. The number of myocardial infarctions (MIs) and rate of pulmonary edema and adult respiratory distress syndrome was less in those patients transfused with less blood or at a lower trigger. A subgroup analysis of patients with known severe coronary artery disease was examined in a separate article. In those patients, blood transfusion did not improve outcome or prevent MIs. Mortality was not different overall but those patients transfused less had a lower rate of multisystem organ failure. (see Table 2).

In summary, the only prospective randomized trials of transfusion

TABLE 2. Results of prospective trial of transfusion(TX) for critically ill patients

Mortality	Restrictive TX (%)	Liberal TX(%)	p value
All patients	18.7	23.3	0.10
APACHE II	8.7	16.1	0.03
<55 years old	5.7	13.0	0.02
Cardiac surgery	20.5	22.9	0.69
Death (in hospital)	22.2	28.1	0.05
Complications			
MI	0.7	2.9	0.02
Pulmonary edema	5.3	10.7	<0.01
Angina	1.2	2.1	0.28
Acute respiratory distress syndrome	7.7	11.4	0.06
Infection	10.0	11.4	0.38

**Data from Hebert et al. 10 Note that either restrictive transfusion therapy produced better outcomes or the groups were equal. Patients with more blood transfusion did not do better by any measure. Note that MI was found less when patients were transfused less.*

show either no difference in outcomes with transfusion or actually better outcomes in those patients receiving fewer transfusions with more conservative transfusion triggers. More randomized control trials in large groups of patients with different disease conditions would be a welcome contribution to an evidence based approach to making transfusion decisions. However, current transfusion practice is so entrenched in our medical education and practice that such studies are often difficult to complete. At a minimum, this growing awareness that transfusion may in fact have significant disadvantages, with few of the assumed benefits, may influence our clinical judgment in this challenging and somewhat murky field.

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New Software Implementation to Streamline Transfusion Services

The Rex Hospital Blood Bank has recently implemented new computer software from Wyndgate Technologies named Safetrace TX for computerized management of the Transfusion Service. The new software replaces our previous system that was in use since the early 1990s. Safetrace TX will improved workflow and enhance safety measures.

The entire implementation team should be recognized for exceptional dedication and hard work on this project. Blood Bank staff and Information Technology staff displayed an amazing and impressive dedication to meeting the demands of this implementation which was accomplished in record time, before our deadline, and in a thorough manner. The fact that our go-live week was rather quiet and uneventful is the best measure of how hard our implementation team worked.

So what does this mean for the rest of the hospital, nursing and medical staff? Well, not too much. Actually the vast majority of the changes will only effect our blood bank staff. However, a few new features will be seen in the medical record and in Clinical Workstation. Rather than being included in the general laboratory results reports, Blood Bank results will appear separately on both a Daily Cumulative chart report and a Discharge Summary Report. Transfusion reaction investigation findings will be reported on a separate Transfusion Reaction Report. Blood Bank results in Clinical Workstation will remain largely unchanged..However, as an enhancement, the actual availability of each blood product will be displayed

Safetrace TX team members shown *(left to right)*: Diane Stephenson, Jeff Hanchet (Wyndgate), Marla Spencer, Dr. Tim Carter, Duwayne Engman and Renee McDade, . Members of the team not shown: Sheila Parker, Judy Allen, Kim Grove, Gov Wallace, Karen Sawyer, Sheila Smithey.

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