Blood Conservation: Why Bother?

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That the blood supply is the safest it has ever been is decried in many academic and lay press publications. Hepatitis and human immunodeficiency virus (HIV) transmission have now been almost eliminated from allogeneic stored blood. The improvement in viral transmission risk has come at a considerable cost. New plagues await the blood-banking industry, and today the country has just survived the scare of West Nile virus infestation of the United States blood supply (1/800–1/4,000 units). In 1 year, a nucleic acid test (NAT) for West Nile virus has been instituted, now rendering the chance of West Nile transmission through the blood supply to a much lower level. New viruses will always be a menace, and viruses such as cytomegalovirus and transfusion-transmitted virus (TTV) are present in the majority of units transfused. However, transfusion medicine is rapidly changing and because hepatitis and HIV have been essentially eliminated from the blood supply, the focus shifted to a number of other crucial and fundamental questions. This supplement to the Journal of Cardiothoracic and Vascular Anesthesia examines some of the issues and encourages methods to conserve banked blood, including perioperative techniques and pharmacotherapies such as aprotinin. This article touches on a number of issues surrounding transfusion, all of which provide the compelling argument that conservation is necessary.

Allogeneic banked blood is a rare and precious commodity. It is a commercial product and is dealt with by the federal government not only as a therapeutic agent (regulated by the Food and Drug Administration [FDA]), but it is also controlled by the Interstate Commerce Commission. As a commercial product, it has a value (cost), is ruled by supply and demand, experiences shortages, and must move through a system of harvest, manufacture, storage, and distribution. All of these areas have micro- and macroeconomic models and implications that this article cannot cover. The physician studying blood transfusion must realize that there are market forces working to control the movement of available blood supplies. Costs are rising as shortages occur.

Clinicians have always accepted that blood transfusion is "good" or that it saves lives. If anything was learned from the crisis of acquired immunodeficiency syndrome (AIDS) and hepatitis in the blood supply, it should have been that transfusions do not always save lives. In some instances, they help to spread disease and can actually be the cause of death. There simply are no conclusive data on the efficacy of blood transfusion. Today clinicians are urged to follow the structure of evidence-based medicine. There are no randomized, double-blind, placebo-controlled trials of blood transfusion versus a placebo. It simply cannot be done ethically.

Transfusion has emerged over time as an accepted practice. There has been relatively little basic science guiding the application of a safe and appropriate trigger for blood transfusion. Therefore, there are huge gaps in the knowledge of when and who to transfuse with how much blood. It may be hard to cope with that fact because transfusion has been such a mainstay of physician practice, but few well-constructed randomized trials of transfusion versus withholding transfusion are available. The trials that do exist amazingly do not show that transfusion, as a therapeutic intervention, improves patient outcome. Indeed, these individual papers and some meta-analyses now show that patients do as well or better if not transfused; and, in some cases, show early mortality if they do receive a transfusion. Microcirculatory and basic science research call into question whether allogeneic stored blood can deliver oxygen to tissues at risk. These data should make the practitioner question longstanding beliefs about a "transfusion trigger." There may not be any good trigger to guide therapy; yet, blood must and surely does save lives, even if there is no agreement on an exact trigger. Banked blood is rare, costly, and there is now uncertainty about when it improves outcome. There should be no doubt that conservation and less liberal utilization should be espoused.

Blood Shortages

Blood shortages are common events today. Almost every city, community blood service, American Red Cross Center, and hospital is experiencing them on a recurring basis. In 2000, the United States Congress commissioned and received a report on forthcoming blood shortages and studied the issues at hand. They are to be commended for trying to anticipate future problems and to prop up the supply side of the equation. Some of the statistics from that report are interesting and staggering. For example, in 1997, more than 12 million units of whole blood were donated by 8 million volunteers in the United States. Approximately 4 million patients received one or more transfusions that year. By the year 2000, it was anticipated that the United States would not be self-sufficient. Indeed, it never really had been. In the latest national report, more statistics are available. These data showed that 27 million units of blood components were collected and 26.5 million units were transfused to 4.5 million recipients. Such a close collection-to-infusion ratio means that at any given time there may be mismatches between need and available supply. Today only 5% of the population able to donate actually does participate.

The greater New York region had always imported blood from Western Europe (mostly France and Germany). With the new variant Creutzfeld-Jacob (vCJD-mad cow disease) situation in the United Kingdom and then all of Europe, importation of blood to the United States was halted. This practice had accounted for between 20% to 25% of New York's blood supply. With that single crisis, New York City became a sink for blood donations on the eastern seaboard. Also, the United States immediately experienced a 2% to 4% deficit in donations versus demand.

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Mad cow disease (nvCJD) has led to further regulations by
the FDA. Initially enacted was a restriction that persons who
lived or traveled to the United Kingdom for longer than 6
months could not donate blood. This regulation was handed
down in August of 1999. It has since become more stringent
and now any person living in Europe for 6 weeks or longer
from 1980 onward must be eliminated from the donor pool.
This essentially eliminates a highly motivated and capable
donor population, returning United States armed forces person­
nel who have served in Europe. It also means that the armed
forces personnel in the countries in question cannot donate for
their own troops, and, therefore, the armed forces become a
further drain on the homeland blood supply. The impact of
these regulations is hard to gauge, but it is thought that the first
regulation in August of 1999 caused a further 2.5% reduction in
the blood supply. The next regulation may also have had about
a 2% impact. Of interest, and at the time of preparation of this
manuscript, there were no recorded cases of nvCJD being
transmitted by blood transfusion; however, there are well over
100 human cases in the United Kingdom, thought to be caused
by ingestion of infected beef. A number of people have re­
ceived blood products, mostly fresh frozen plasma, from do­
nors who later went on to have nvCJD. The disease takes years
to decades to manifest itself. Furthermore, the United Kingdom
has very recently reported a case of possible transmission of
nvCJD in a transfusion recipient. Is the United States being
foolish or prudent with its regulations? What will be the effects
of mad cow disease being found in the United States in 2004?

The donor pool within the United States is shrinking. As
stated earlier, only 5% of the available donors are involved in
supporting the nation’s blood supply. Donors in the past have
been voluntary, altruistic people motivated largely by the pub­
lit relations campaigns of the Red Cross and the regional/local
blood centers. To have people volunteer it is necessary to make
them feel good about what they are doing. The industry has
grown out of plasma drives during World War II wherein
making human plasma available to trauma victims at the front
may well have saved lives. 7 Fresh whole blood was the trans­
fusion of choice during that conflict. Today, untrue or stretched,
but very popular statements are made every day to motivate the
public. One of the more common ones is, “Last year 4 million
lives were saved by blood transfusion.” It is simply not known
how many people’s lives were saved by blood transfusion.
Notably, the same number as people who received a unit or
more of blood is what the Red Cross quotes. The segment of
society with the highest donor percentage is now aging and
dying. Those persons were alive during the Second World War
and the Korean conflict. Their numbers are dwindling, and
generation “X” appears much less altruistic or motivated to
donate.

The AIDS and hepatitis crisis have in themselves decreased
donations. There is not a shred of evidence that blood donation
can lead to contraction of one of these diseases, but some
donors simply do not understand that. Furthermore, some pre­
vious donors find the frankness required in questioning about
voluntary withdrawal from donation to be offensive. As one
elderly donor has expressed, “The questions being asked now at
my blood donation center are so offensive I simply do not want
to go there and donate anymore.” This man had donated more
than 11 gallons of blood during his life and now had voluntarily
withdrawn because he did not want to be asked about homo­
sexual or illicit sex acts. Between 1994 and 1997, this led to a
5.5% decrease in donations. 8 Since that time, donations have
continued to decline. Furthermore, about 2% of all units are
rejected during testing. That number has since increased now
with NAT and will further increase with West Nile virus NAT
testing. It is hard to tell exactly how far down the blood supply
has gone, but since the early 1990s, it is safe to say that there
is at least a 10% reduction in blood supply and a 15% reduction
is probably realistic. There is no projection of where that will
stop or even level off.

Meanwhile, the demand for blood has increased. Yearly
increases in demand have been the routine since the mid 1980s.
In the same period from 1994 to 1997, as supply fell 5.5% from
decreased donation, demand rose 3.4%. 8 The forces causing
this are more complex surgery (liver, heart, lung transplanta­
tion, aortic surgery), more aggressive treatment of cancer (eg,
bone marrow transplantation), and a general belief that trans­
fusion improves outcome. The population is aging, and there­
fore those patients who had previously been donating blood to
the pool are now becoming the patients requiring more ad­
vanced and invasive procedures. These trends will not stop and
will likely accelerate in the next 25 years, with perhaps the
majority of the population being over 50 years of age by the
year 2030. The problems of blood shortages will therefore
become significantly worse. Blood shortages are here to stay.

The impact of blood shortages is just beginning to be felt.
Elective surgeries have been canceled in a number of cities
because of crises events.11,12 Such cancellations lead to conflict
within hospitals as surgeons deal with rescheduling their cases
and turn to the transfusion services to find fault. Fault is not
there or it is so widespread that the entire infrastructure of
medicine needs to be examined. Rescheduling of surgeries has
significant financial implications. Lost time for operating room
productivity, personnel without cases to perform, and instru­
mants and expensive equipment lying idle all have inherent
costs that have not yet been modeled into the effects of blood
shortages. Patients take time off from work and find child care,
and, when their surgery is canceled, these have to be resched­
uled and all have costs to society.

Interestingly, the report to Congress in 2000 made little
mention of blood conservation. It recommended increasing
supply and harvest of blood by a number of means but noted
that employment of transfusion specialists to change physician
behavior was too costly and beyond the capability of most
hospitals. Because there was a shortage of transfusion specialist­
s, they felt large-scale re-education was not reasonable. They
did little to recommend conservation or changing the transfu­
sion triggers. They did not even mention any basic science or
further studies to more clearly define when transfusion was
appropriate or most useful. 8

COSTS

It is very hard to get a handle on exactly what a unit of
allogeneic blood costs. As stated earlier, shortages lead to
widespread economic implications, all of which have been, at
best, incompletely modeled. It can be shown what a patient is
billed for a unit of blood, but there is a great deal of variability
today and ranges between approximately $100.00 to $350.00 per unit. The factors leading to that variability are what would be expected simply from standard economic models. Supplier makes a difference and some blood centers are surprisingly inexpensive, whereas the Red Cross tends to be more expensive. Certainly, supply and demand will drive these costs/billings in the future. As blood becomes more scarce, it will cost more.

The institution of NAT testing for HIV and hepatitis has added approximately $8.00 to $15.00 to the cost of each unit.\(^{14}\) With the addition of NAT testing for West Nile virus in 2003, another $8.00 to $15.00 per unit cost has also been added. The cost of adding universal leukoreduction could be very large; filters alone range from $35.00 to $45.00 each.\(^{14}\) These filters must be used at the time of harvest. It is estimated that 1% to 2% of the blood supply will be lost by universal white cell reduction, and that cost has not been calculated into the economic models. If the cost per unit harvested times the cost per leukoreduction filter is multiplied, almost $500,000,000 of added cost is incurred. There is a mind set among the transfusion community and the FDA that the country must have the safest blood supply possible at any cost.\(^{15}\) That is admirable (safety of the blood supply), but there is no cost analysis involved, and it is quite probable that by the year 2010 a $500.00 unit of blood will be commonplace.

The cost of a unit of blood is not just the acquisition cost (the price paid by the hospital or individual to the regional supplier). Running a hospital blood bank and distribution network throughout the hospital requires personnel, storage refrigerators, crossmatch laboratories, and hospital infrastructure to move blood, record its usage, and deal with problems. It is costly to maintain such a service, and it has been estimated that these fixed overhead costs add approximately $285.00 per unit.\(^{14}\) That is, of course, an estimate, and each unit of blood saved cannot directly translate into a $285.00 savings to the hospital. Indeed, some would say that by reducing the number of units put through a system, there is a loss of scale, and, therefore, the cost per unit might actually increase. Until blood use reductions are enough that personnel can be moved elsewhere, let go, or the entire system within a hospital downsized, these are truly fixed costs.

A unit of blood carries risks. Focus has been on the risks of viral transmission, particularly AIDS and hepatitis. Estimates of the economic costs of these viral infections have been created from computer models.\(^{15}\) Those computer models were created to contrast the costs of autologous blood versus allogeneic blood. The initial models created found that the risk of any individual patient contracting HIV or hepatitis was so low that the incremental cost per unit of blood (for the risk of HIV and hepatitis) was correspondingly low (less than $1.00/unit). Therefore, these computer models noted that the per unit cost to save a human life (quality adjusted life-year) of autologous blood was extremely high and unjustified (between $500,000–$1,000,000).\(^{15}\) These models only took into account HIV and hepatitis, not all the other potential adverse events of blood transfusion.

A more recent re-examination of this economic modeling included the effects of perioperative immunosuppression leading to an increased risk of perioperative infection.\(^{16}\) Infection after surgery can be devastating and costly. It has been estimated that nonwhite-cell-reduced red cell transfusion can increase the risk of major infection between 1.3- to 3.6-fold.\(^{15,22}\) That has been translated into a per unit increased cost of treatment and hospitalization of more than $800.00.\(^{16}\) This estimate again falls short of real macroeconomic costs. It only puts numbers on the treatment time in the hospital, not long-term rehabilitation, loss of time from work or death, or other family members losing time at work. One estimate of the risk of pneumonia after cardiac surgery is that it increases by 5% per unit transfused.\(^{23}\) Notably, none of these estimates takes into account the costs of ABO-ri incompatibility (1/6000-1/20,000 units), graft-versus-host disease, transfusion-associated lung injury, allergic reactions, fever, alloimmunization, difficulty crossmatching for organ transplantation, hypotension, renal failure/injury, and other complications. Each has a cost per unit and, because people have estimated the incidence of each event's occurrence, it would be possible to create a larger model that gives an estimate of the added risk cost per unit of blood. It is fair to state at this time that the real cost, adding acquisition, fixed overhead, and risk costs of a unit of allogeneic banked blood exceeds $1500.00 per unit. Therefore, transfusion is one of the most costly routine therapies used.

**EFFICACY**

Blood transfusion, even though very costly and scarce, might well be worth it if it was known when it was efficacious. Unfortunately, the practice of transfusion has arisen over time and evolved with the development of modern medicine. It has never been put through the rigorous testing of an FDA approval (even though it is regulated by both the FDA and ICC). Physicians transfuse an individual patient because they believe the patient is in impending danger if they are not transfused or do so based on the belief that the patient will benefit from the increase in oxygen-carrying capacity. It is a practice of prophylaxis, and, therefore, it is today thought to be unethical to randomize a group of patients to not be transfused. Therefore, researchers cannot do placebo-designed true efficacy studies in any group of patients. However, clinicians have learned a great deal about transfusion both from animal models and from some fairly recent prospective randomized trials of liberal (more common) and restrictive (radical) transfusion therapy. As well, data exist from a growing database of Jehovah's Witness patients who have undergone a number of medical procedures without transfusion. Therefore, the data available are not perfect, are inferential on many occasions, and do not fit all the criteria for pure evidence-based medicine.

Historically, the transfusion trigger hemoglobin level has been 10 g/dL.\(^{24}\) This number, although easy to remember, is not based on any animal or human research. It evolved out of opinions from leaders in the fields of surgery and anesthesiology. It is known from both animal and human research that the critical hemoglobin (that level at which compensatory mechanisms are exhausted, and metabolism switches from aerobic to anaerobic) is approximately 3 to 4.5 g/dL.\(^{25,27}\) Because transfusion is a prophylactic therapy, there is no way that physicians will wish to take patients to their critical level each time. Interestingly, it is at that level (between 3-5 g/dL) at which Jehovah's Witness patients begin to experience an increased
mortality. A commonly held belief, but one with scant data, is that patients with more serious or extensive systemic disease (eg, atherosclerosis, hypertension, diabetes, and so on) could benefit from a higher transfusion trigger. Clinicians simply do not know if this is true or not. It is entirely possible that the exact opposite is true in that patients may do worse or be prone to more complications of transfusion if they have systemic disease. Clearly, more research is needed.

Recently, a number of studies have begun to appear wherein transfusion and outcome have been examined. These studies for the most part have not been very large. One study examined more than 800 patients in the critical care setting. These patients were randomized to be transfused at between 9 to 10 g/dL or at 7 g/dL. They had a wide range of very serious and life-threatening diseases. Some had acute respiratory distress; a number had evolving myocardial infarctions, sepsis, gastrointestinal bleeding, congestive heart failure, and other conditions. Interestingly, nowhere did the data show that those who were transfused did better. Either there was no difference in outcome or the patients with the more restrictive transfusion algorithm had fewer complications. A subset of more than 300 patients with known cardiac disease was carefully examined. There were no real differences in outcome other than those who received less blood transfusion had fewer reports of multiple organ failure. Two recent meta-analyses have shown that either patients receiving fewer transfusions do better or show no difference from those transfused. An editorial in the British Journal of Anaesthesia examined the evidence for blood transfusion and concluded that fresh whole blood will deliver oxygen well; however, there are no industry and infrastructure to provide that to practitioners. They also concluded that the data showing that aged banked blood is helpful are not conclusive.

Considerable work has been done on the microcirculation and examining the effects of storage upon red blood cells. Storage lesions begin immediately and within 24 hours the blood is acidic, has lost a great deal of its 2,3 diphosphoglycerate (2,3 DPG), has decreased cell flexibility, and actually loses cell membrane material. The biochemical and physiologic effects of storing blood are complex, and this introductory material cannot go into great detail. However, at 28 days of storage, banked blood is profoundly acidic, hyperkalemic, without calcium or magnesium, and filled with cytokines, bradykinin, complement, cell fragments, and lipids. When infused, it blocks the microcirculation, and, even under the best of circumstances, the red blood cells cannot take up and release oxygen in a normal manner. The severe depletion of 2,3 DPG makes the hemoglobin hold on tightly to oxygen. Perhaps it actually pulls oxygen from surrounding normal cells or from its target tissues. With time, the erythrocytes regenerate 2,3 DPG and biochemical processes begin to normalize. However, there are data from both cardiac surgical and critical care patients that show infusions of banked blood adversely affects the delivery of oxygen to critical tissues.

Therefore, the basic tenet of blood transfusion is called into question. Is tissue oxygen delivery actually improving with any single unit of blood from the blood bank? The evidence would seem to point toward a conclusion that, at least in the very acute early posttransfusion period, oxygen delivery is not improving. With those data in mind, when should patients be transfused? It seems there is no right answer to that question at this time. The data from the outcome studies would suggest that it is at least safe to transfuse less than is being done today.

CONCLUSIONS

The case for conservatism is compelling. It is not known exactly when the therapy is efficacious. There is a widely held belief that blood does some good, but the science says perhaps that is not so. There must be a time or point at which blood transfusion does save lives and perhaps that is when there is massive bleeding or when that critical shift point has been reached. However, it is clear that banked blood today is costly and will become even more costly because its scarcity will continue or get worse in the future. Blood conservation, withholding transfusion, finding ways to conserve the patient's own native red blood cells, or boost production and decrease bleeding all make sense so that there can be more of the rare and precious banked blood available for those patients who can truly benefit. Now all that is needed is the further research and science to understand which patients can derive benefit from transfusion.

REFERENCES


22. Dzik WH: Mononuclear cell microchimerism and the immunomodulatory effect of transfusion. Transfusion 34:1007-1012, 1994


