Transfusion Medicine

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Abstract

Far-forward blood transfusion is a controversial topic. Transfusion of stored packed red blood cells (pRBCs) has come under increasing scrutiny in civilian trauma centers and may have fewer benefits than previously believed. The unnecessary transfusion of stored blood products has the potential to do significant harm, particularly when the blood has been stored for the long periods typically seen in the combat theater. Therefore, when transfusion is considered for an acutely injured patient, careful attention must be paid to the risks, benefits, and indications for transfusion. Once transfusion therapy is chosen, the provider must carefully adhere to established guidelines and procedures to minimize potential harm to the patient.

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Objectives

1) Identify the known adverse outcomes with the use of blood products.
2) Define the indicators for blood product transfusion.
3) List the common transfusion reactions and how to treat them.

Introduction

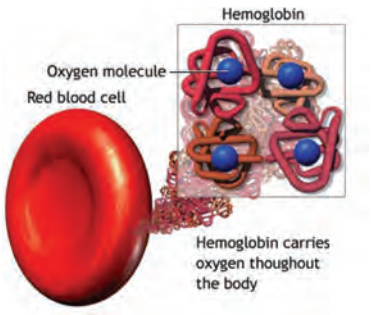
Throughout Operation Enduring Freedom and Iraqi Freedom, blood products have been available on the battlefield. Within the Special Operations environment, there has been great debate as to where the administration of these products could have the greatest benefit for our casualties. Anecdotal reports indicate that blood products are being administered far-forward in anticipation of shock, rather than as treatment when shock exists. Unfortunately, aside from the significant technical complexities of administering blood products far forward, there appear to be significant downsides to giving blood products to our patients. This is particularly true when blood products are given before they are absolutely necessary. When hemorrhagic shock that is unresponsive to fluid resuscitation exists, transfusion is clearly indicated. Giving blood products prior to that point, however, may actually be detrimental to our patients.

Many of the anecdotal benefits that exist with normalizing a patient's hemoglobin/hematocrit with pRBCs have not shown benefit in the current literature. As a result, many regional trauma centers have chosen to institute restrictive blood product protocols to minimize the many adverse effects. This shift to evidence-based practice in the hospital environment initiated more analysis of the cost-benefit relationship of the early utilization of these products. No prospective trials of administration of blood products in the far-forward setting exist, but study of the available literature on transfusion provides sensible conclusions for the use of blood products in the far-forward setting.

In view of the current practices of hypotensive resuscitation and tactical combat casualty care, a well researched, critical look at blood product placement and usage in the far-forward Special Operations environment is warranted. This article will review current literature on the topics published in the English medical literature. We will review the effects of blood storage and the current theories that account for some of the observed adverse effects. We will also discuss whole blood transfusion and potential blood replacements. We will finish with a review of suggested guidelines for administration, procedure, and hazards of blood administration in the far-forward environment.

Ex Vivo Blood Storage

The effects of blood product storage greatly influence its value during transfusion. The modern blood bank system has greatly extended the availability of blood products to the population, but the storage techniques have changed little since the 1940s. Storage of RBCs causes a number of morphologic and biochemical changes, which are only partially accounted for in the way that we measure post-transfusion RBC viability. We currently evaluate the viability by the post-transfusion RBC survival. This current standard is an arbitrary value of greater than 70 percent RBC integrity at 24 hours. Originally, this was deemed to be the value that would most reflect the measured hemoglobin and hematocrit post transfusion. Current authorities, however, would debate that this was the only achievable percentage at the time. There are no clinical outcome variables attached to this number or followed after its institution. Thus, while using this measurement improved the patient's lab values, the overall clinical benefit was never shown. Currently, RBCs stored up to 42 days maintain their 24-hour post-transfusion viability.[1]



The RBC is a highly specialized cell which can deliver oxygen to and remove carbon dioxide from the body. Its shape and deformability allow it to traverse the capillaries and microcirculation without structural or functional disruption. During storage, however, the RBCs are deprived of adenosine triphosphate (ATP), their energy source, and undergo many morphologic changes. Cytoskeletal protein loss forces the RBCs to lose their biconcave shape and thus limit usable surface area for gas exchange. They also lose surface sialic acid and membrane lipids. The loss of these membrane components results in an increase in the aggregation of the RBC and limits their deformability. Furthermore, through the loss of cellular antioxidants, hemoglobin is converted to methemoglobin which is incapable of binding oxygen. Finally, 2,3 diphophoglycerate (2,3 DPG) is depleted by the storage medium and subsequently decreases the existing hemoglobin's affinity for oxygen. This results in a decrease of the stored RBCs' ability to exchange gas and deliver oxygen through the microcirculation to the tissues.[2-32]

Packed RBCs represent only a portion of the whole blood that is initially collected. Plasma and platelets are removed in the processing prior to RBC storage. Though many elements are removed from the whole blood, the RBC component is far from pure. It contains many cellular components and bioactive substances, some of which are thought to contribute to many of the adverse

effects seen in the transfusion of stored RBCs. The increased presence of white blood cells in the RBC medium contributes significantly to RBC destruction and the subsequent leakage of potassium (K+) from the lysed cells.[33] Leukoreduction prior to storage has reduced, but not eliminated, this effect.[34]

Many of the remaining bioactive substances in the medium also adversely affect the RBC performance and limit the overall effectiveness of transfusion. These substances include histamine, lipids, cyotokines, fragments of cellular membranes, and human leukocyte class I antigens.[35-38] Some of these cytokines significantly contribute to the non-hemolytic febrile transfusion reactions seen in many patients. These reactions can be reduced, but not eliminated, with pre-storage leukocyte depletion.[39-42] The soluble lipids present in the medium are thought to contribute to increased platelet aggregation and host neutrophil activation.[43-46] Since these substances are not products or byproducts of white blood cells, leukodepletion does not reduce the incidence of side effects. In addition, many of these bioactive substances are thought to exist in levels high enough to produce systemic inflammatory responses. This inflammatory response is the current mechanism thought to produce much of the rise in morbidity and mortality seen in the utilization of stored RBCs.[47]

CLINICAL EFFECTS OF BLOOD LOSS

Anemia and Mortality

A substantial difference exists between clinically significant and diagnostic anemia. A healthy human is amazingly tolerant to the anemic state. Physiologic compensatory mechanisms, such as increased cardiac output and oxygen extraction can more than compensate for non–hemorrhagic shock levels of anemia. Normovolemic anemia to levels of 3.5 to 5.0 g/dL of hemoglobin has been shown to be adequate for organ perfusion.[48,49] As mentioned above, the logic of correcting anemia with RBCs has never been shown to improve oxygen availability or overall clinical benefit.[50-53] Evidence now exists of an overall harmful effect when patients are transfused to the previous standard of hemoglobin of 10g/dL.[54] The caveat to this, of course, is the adult with underlying cardiac dysfunction. A myocardial basal oxygen extraction rate of 55 to 70% leaves little capacity for improvement.[55] Thus, the only existing compensatory mechanism is increasing the coronary blood flow. This presents a particular problem for patients with baseline coronary artery disease. Several studies in the surgical literature show an increased post-operative mortality in these patient populations secondary to anemia.[56,57] One study, however, showed no discernible difference when stored RBCs were used to correct an underlying anemia.[58] This adds momentum to the rise of cell saver technology and autotransfusions of the patient's own blood during operative interventions. Thus, there is currently a lack of evidence to support transfusions in healthy anemic patients without evidence of organ dysfunction or hemorrhagic shock.

Population Based Studies of Adverse Outcomes

Two large population based studies have reported that transfusions alone are an independent risk factor for death.[59,60] Three retrospective and one prospective study in critically ill intensive care unit (ICU) patients show an increase in morbidity and mortality associated with transfusions alone.[61-64] This culminated in the landmark Canadian study showing the use of restrictive blood protocols increased survival in an ICU setting.[65]

Adverse clinical outcomes with the use of blood products include increased mortality, increased hospital length of stay, multiple organ system failure, increased infections, and impaired tissue oxygen utilization. Incidence of these ill-effects correlates with the age of the stored blood.[66-73] A prospective cohort study of 513 trauma patients found that transfusion is an independent risk factor for post-injury multiple organ failure. There is also an association between the number of units transfused in these patients and the number of complications.[63] Another study in trauma patients by Zallen et al. demonstrates that the mean blood age, number of units greater than 14 days old, and the number of units greater than 21 days old are also independent risk factors for multiple organ failure.[74] The many studies of post-coronary artery bypass graft (CABG) patients have shown similar effects to those as seen in the Zallen et al. study.[75-78]

A correlation between infections and blood product administration similarly exists. As described earlier, transfusion with allogeneic blood products expose the patient to large amounts of cellular and antigenic compounds, as well as bioactive substances that increase proinflammatory and immunosuppressive responses. TRIM, or transfusion related immunomodulation, is a theory first described by Opelz et al. that may explain some of the increased morbidity associated with transfusions.[79] Transfusion of pRBCs appears to cause transient suppression of the immune system. Immunosuppression after

RBC transfusion was initially found to be beneficial in recipients of cadaveric kidney transplants, but was also later found to be associated with increased rates of post-operative infections. Immunosuppression may therefore play a significant role in the increased rate of infection in patients who have received transfusion.[80-83] A prospective cohort study of trauma patients demonstrated that transfusions of RBCs stored greater than 14 days and 21 days are independent risk factors for post injury infection. The risk increased 13% for each unit that was greater than 14 days old.[84] Although this effect would not be seen on the battlefield, it is certainly cause for concern.

Finally, there is doubt as to whether the administration of red blood cells significantly increases the oxygen consumption capabilities of the body. Studies looking into the oxygen utilization pre- and post-transfusion show mixed results. Multiple studies clearly demonstrate that administration of older blood products decreases the oxygen consumption capabilities of the body.[85-90] Thus, the clinical benefit from blood more than 14 days old seems limited, and the potential for multiple adverse events actually increases.

Whole Blood Transfusion

The use of fresh whole blood for transfusion has largely ceased in the civilian sector, but continues to be utilized in the management of combat trauma in theater. Because of the lack of use in civilian medicine, however, a lack of outcome data exists to support or refute the use of whole blood transfusion. The majority of recent literature focuses on the utility of whole blood to augment component therapy in austere locations. Recent reports suggest whole blood has a role in the resuscitation of patients requiring massive transfusion (>10 units pRBCs) and others have used whole blood successfully when transfusion services and component therapy were exhausted or unavailable.[91-93]

In theory, the use of whole blood overcomes the limitations inherent in blood component therapy used in theater. When taken from a prescreened, walking donor pool, whole blood may provide significant benefit due to its lack of storage and avoidance of the aforementioned loss of efficacy in component therapy subjected to long storage times. Furthermore, the use of whole blood anecdotally provides rapid reversal of coagulopathy, an attractive feature particularly in combat when the patients are often hypothermic and have a resulting coagulopathy.[93]

Limitations to the use of whole blood are primarily related to the transmission of infectious disease, notably hepatitis C and HIV.[91] Current risk of transmission of hepatitis C from screened civilian populations is estimated to be 1 in 1.4 million, with the HIV transmission risk estimated to be 1 in 1.6 million.[94] While these risks are probably lower when blood is taken from the screened military population, the true risks are unknown.

Secondary risks include transfusion reaction, particularly when type-compatible, uncrossmatched blood is used in the emergency setting. Again, the true risk is unknown, but data from the use of whole blood in massive transfusion suggest the risk to be approximately 9%.[95]

At this point the use of whole blood in the far-forward setting should be considered experimental at best. The benefits of whole blood are attractive, particularly in theater when component pRBCs are often old and in limited supply, but the rate of transfusion reaction, the possibility of infectious disease, and the lack of proven benefit in controlled trials suggest whole blood use should be limited to the hospital/Level III setting where it can be used in a controlled fashion and studied prospectively. Using whole blood transfusion when hemorrhagic shock has not yet occurred is clearly not yet indicated and could be harmful.

Blood Substitutes

The promise of blood substitutes has kept Medics, doctors, and stock investors salivating for the last two decades. Blood substitutes would appear to be the ideal solution to many of the problems of both stored RBCs and transfused whole blood. The ideal blood substitute would eliminate the possibilities of allergic reactions, transmission of infectious disease, and would provide for long storage. All of these qualities would make blood substitutes ideal for use on the battlefield and in austere conditions. The focus of most recent research and development has been in the area of hemoglobin based oxygen carriers or HBOCs. In theory, HBOCs provide all of the desired qualities for a suitable blood replacement. Unfortunately, none have so far proven to be safe for use in humans.

Numerous attempts have been made to synthesize a solution that would allow delivery of oxygen to ischemic tissues. Recent history is littered with prospective solutions to the complex problem of oxygen delivery. Most of the recent attempts, however, have narrowed to a select few compounds that are based on hemoglobin molecules. Ideally, recombinant human DNA would be used to manufacture hemoglobin. Unfortunately, this has proven to be prohibitively expensive. Clinical trials are ongoing to evaluate the use of blood

substitutes, but recent data have been somewhat discouraging. The recent disclosure of increased mortality in patients treated with the blood substitute Polyheme® in a large prospective trial comparing the blood substitute to standard treatment has dampened enthusiasm for blood substitutes and made it unlikely they will be available for use in the operational setting for the foreseeable future.[96]

Transfusion Indicators and Procedure

Guidelines for the use of blood products in Special Operations exist.[97] These guidelines provide an easy framework for determining if blood products should be given. We suggest that stored, pRBCs should only be given under very isolated and precise circumstances. If the established protocols are not followed, the potential for doing great harm is high.

Transfusion should only be considered if the patient is in Class III or IV shock, as manifested by signs and symptoms consistent with blood loss greater than 1500cc. In the case of bleeding controlled with a tourniquet or hemostatic dressing, the appropriate indicator is persistent hypotension and tachycardia despite resuscitation with 500cc of Hextend®/Hespan® or two liters of normal saline (NS). If bleeding cannot be controlled (thorax, abdomen), transfusion should be considered when evidence of end-organ dysfunction exists and hypotensive resuscitation with Hextend/Hespan or NS fails to correct the end-organ dysfunction. Indicators of impaired end-organ perfusion include altered mental status/confusion in the absence of head injury, weak or absent radial pulse or pulse-oximetry readings of less than 90% with a good waveform and no chest injury. Transfusing in anticipation of these conditions may ultimately be harmful due to the many factors detailed in this review.[98]

Once transfusion has been selected, proper procedure must be followed to minimize the possibility of harm. Before beginning transfusion, ensure the patient has suitable intravenous (IV) access with an 18G catheter, as an absolute minimum. Once IV access is secured, obtain baseline vital signs and inspect the blood products. The responsible provider must ensure that the unit selected for transfusion is of type "O" only, is not expired, and does not appear to have any contaminants or air present. After the unit is inspected, Y-type blood tubing must be used for transfusion. The unit of blood is spiked with the line and a bag of NS MUST be used in conjunction with the unit of pRBCs. Prime the infusion set with NS and attach to the IV catheter. Once the infusion set is in place, administer the pRBCs by gravity flow for the first five minutes. Once it has been determined that no reactions have occurred, the blood should be given as rapidly as possible with a pressure bag at a pressure of 250 to 300mmHg. If any evidence of a transfusion reaction occurs, stop the infusion immediately and keep the unit with the patient for further evaluation once definitive care is reached.[98]

Transfusion Reactions

Once transfusion has been initiated, it is of critical importance to monitor the patient very closely for the occurrence of a transfusion reaction. The most serious complication of transfusion therapy is a hemolytic reaction which can result in serious, if not fatal, complications. If ABO-incompatible blood is given, the recipient's ensuing immune reaction will result in immediate destruction of the donor RBCs and a systemic immune response leading to worsening hypotension, renal failure, respiratory compromise, and/or disseminated intravascular coagulation.[99]

Symptoms of hemolytic transfusion reactions include fever, dyspnea, low back pain, worsening tachycardia, and hypotension. If symptoms of a hemolytic reaction occur, it is of critical importance to immediately stop the transfusion, monitor the patient's vital signs, and provide immediate resuscitation with normal saline. Airway control may be necessary and urine output should be monitored closely to maintain a rate of at least 100cc/hour.[99]

In the far-forward setting it may be difficult to differentiate less serious transfusion reactions such as a febrile reaction due to persistent leukocytes in the donor blood or a minor allergic reaction. In such cases, symptoms will be similar to a hemolytic reaction but less severe. Febrile reactions typically occur in a somewhat delayed fashion with fever, chills, and headache, but do not result in hypotension. Allergic reactions present with hives, chills, fever, flushing, or respiratory distress, and can become severe. Regardless of the suspected cause, the treatment in the operational environment is the same. The first priority should be to stop the transfusion and then manage the effects. Simple febrile reactions can be treated with acetaminophen. Diphenhydramine (Benadryl®) may be useful if an allergic reaction is suspected. If the reaction progresses, it is essential to provide supportive care and treat for anaphylaxis with epinephrine. Once the patient's condition is stabilized, be sure to keep the unit of blood with the patient for further evaluation and testing, once definitive care is reached.[98,99]

Discussion

There is little debate as to the effectiveness of blood transfusion in hemorrhagic shock patients. There seems to be a trend; however, in our combat environment to anticipate hemorrhagic shock, particularly when CASEVAC or MEDEVAC transport is involved. Giving blood products in the anticipation of hemorrhagic shock or for the correction of anemia in previously healthy and compensated trauma patients is clearly unwarranted and likely harmful to the patient. Couple this with the fact that since almost all of our blood products in theater are over 14 days old, the risk of harmful effects is even greater. While the use of whole blood is promising, its use has not yet been proven to be beneficial and also has significant associated risk. Like any medical intervention, giving blood products has advantages and disadvantages. Knowledge of the indications and precautions is essential in order to minimize adverse events and effects. Blood administration in the far-forward environment is technically difficult and predisposed to incorrect technique. This, in conjunction with the above mentioned multiple adverse effects on the patient when blood is given inappropriately or to early, produces a cost-benefit ratio which simply does not justify the use of currently available blood products in anticipation of hemorrhagic shock.

Clear guidance exists in both the Advanced Trauma Life Support (ATLS) manual and current literature as to when stored RBCs are indicated in trauma patients. This article is not intended to dissuade anyone from using stored RBCs in these settings. The intention is to ensure that all providers are aware of the adverse affects of giving stored RBCs and the direct correlation to negative outcomes seen when they are given to patients inappropriately. It is critically important to *only* administer blood products when clearly indicated and to follow correct procedures when choosing to administer blood in the far-forward setting. It is not only by the enemy's hands that our compatriots die. First, do no harm.

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