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Massive Transfusion for Trauma is Appropriate

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Learning Objectives: 1) To review the history of blood transfusion and the science of blood banking. 2) To review the literature regarding massive blood transfusion and outcome. 3) To understand adverse consequences of massive blood transfusion, including hemostatic, metabolic, electrolyte, and immune. 4) To understand the epidemiology, pathogenesis, clinical manifestation, and treatment of transfusion-related acute lung injury. 5) To review an example of a massive transfusion protocol and understand when to activate such a protocol, and who should be responsible for activating the protocol.

Abstract

The history of blood transfusion dates back to the mid-17th century. Scientific advances in transfusion therapy still persist today. Major developments have included blood typing, preservation, storage, fractionation, and the emergence of component therapy. Although early reported survival rates following massive transfusion were dismal (6.6%), recent literature shows survival rates of 40% to 60%. Improved survival has been attributed to improvement in trauma care provision, improved rewarming techniques, damage control celiotomy, and improved blood banking technology. With massive transfusion, the recognition of blood as a form of temporary organ transplantation has been realized. The adverse consequences associated with massive transfusion are now diagnosed and treated earlier. This article reviews the history, outcome, and potential complications associated with massive blood transfusions.

History of Blood Transfusion and Component Therapy

The history of blood transfusion dates back to 1628 when William Harvey, an English physician, discovered the circulation of blood (Table 1). Soon thereafter, the earliest known blood transfusion was attempted. The first successful blood transfusion occurred in 1665, and the first claim of successful human blood transfusion was made by the American physician Philip Syng Physick in 1795. Later milestones include the first successful whole blood transfusion, antiseptics to control infection during transfusions, and saline as a “blood substitute.”

Although blood transfusions were becoming more common, the adverse consequences arising from donor-recipient incompatibility

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Table 1. History of Blood Transfusion

Year	Discovery
1628	William Harvey demonstrates circulation of blood
1665	Richard Lower performs first blood transfusions
1795	Philip Syng Physick performs first human blood transfusion
1867	Joseph Lister formulates antiseptic theory
1901	Karl Landsteiner identifies human blood groups
1912	Reuben Ottenberg coins terms "universal donor" and "universal recipient"
1914	Richard Lewisohn reports use of citrate for long-term blood anticoagulation
1915	Richard Weil develops refrigeration and storage of blood
1932	First blood bank established
1939-40	Karl Landsteiner, Alex Wiener, Philip Levine, and R. E. Stetson discover Rh blood group system
1953	Carl Walter and W. P. Murphy invent plastic blood bag
1971	Hepatitis B surface antigen testing begun
1990	Blood tested for hepatitis C

were not fully understood. In 1900, Karl Landsteiner discovered the three human blood groups, A, B, and O. His colleagues, Decastello and Sturli, added the fourth group, AB, in 1902. Reuben Ottenberg performed the first blood transfusion using blood typing and cross-matching in New York. He also recognized the mendelian inheritance of blood groups and the universal utility of group O donors. The terms "universal donor" and "universal recipient" were not coined until 1912.

The next major advance in transfusion medicine occurred with the development of long-term anticoagulants such as sodium citrate, which allowed extended preservation of blood. This immediately transformed transfusion from a direct to an indirect procedure. At the same time, Richard Weil developed procedures for refrigeration and storage of anticoagulated blood. The addition of a citrate-glucose solution extended the viability of collected blood to several days.

The ability to preserve blood for longer than a few hours led to the first blood bank being established in a Leningrad hospital in 1932. This first blood bank ushered in the science of blood banking and processing. In 1953, a greater level of sophistication was achieved with the development of the plastic blood bag, which was invented by Fenwal Laboratories. The bag made it feasible to fractionate and use the blood's various components.¹

Why fractionate blood? Fractionation allows a specific product or coagulation factor to be transfused with less volume. Different blood component products also require different storage temperatures; therefore, fractionating blood allows more effective storage and product management.

The technique for fractionation is as follows: whole blood is centrifuged at 5000 g × 5 minutes at 4°C ("hard spin") resulting in fractionation of the blood into red blood cell concentrates and plasma. If platelets are required, centrifugation must take place at 22°C and a "soft spin" (2000 g × 3 minutes) is used. This provides an additional fraction in the form of a platelet-rich plasma. Further therapeutic components can be extracted by applying "flash-freezing" technology to plasma. For instance, if plasma is flash-frozen and thawed for 12 to 18 hours at 4°C, most of the plasma becomes liquid, and cryoprecipitated factor VIII is generated. In summary, traditional fractionation yields a number of useful products: red blood cell concentrates, "packed" red blood cells, platelet concentrates, liquid plasma, frozen plasma, fresh-frozen plasma, cryoprecipitated factor VIII, and cryo-poor plasma.²

Blood Component Therapy and Transfusion

Fractionation of blood has led to blood component therapy. In 1994, the American Society of Anesthesiologists established the Task Force on Blood Component Therapy to develop an evidence-based approach for transfusing red blood cells, platelets, fresh-frozen plasma, and cryoprecipitate in the setting of perioperative and peripartum needs for transfusion. The main conclusions were that red blood cell transfusions should not be dictated by a single hemoglobin "trigger value," but instead should take into consideration the patient's risks of developing complications of inadequate oxygenation.³ The factors that determine the risks of bleeding in surgical and obstetric patients depend on the extent and type of surgery, the ability to control bleeding, the actual and anticipated rate of bleeding, and the consequences of uncontrolled bleeding.

The task force also addressed the issue of microvascular bleeding, which is pertinent to the trauma patient with massive transfusion requirements. Platelet transfusion was determined to be ineffective when thrombocytopenia was caused by increased platelet destruction (i.e., idiopathic thrombocytopenic purpura). Microvascular bleeding usually requires platelet transfusion if the platelet count is less than 50,000/liter and rarely requires therapy if it is greater than 100,000/liter. Fresh-frozen plasma is indicated for microvascular bleeding when prothrombin and partial thromboplastin times are >1.5 times normal. Cryoprecipitate is used for bleeding patients with fibrinogen levels below 80 to 100 mg/dL as determined by a disseminated intravascular coagulation panel. Careful adherence to these guidelines for blood component therapy should minimize the incidence of adverse transfusion reactions.

Patient Outcomes Following Massive Transfusion

The most frequent indication for massive blood transfusion is hypovolemic shock secondary to blood loss. This is most often seen in the setting of trauma, ruptured aortic aneurysm, massive gastrointestinal hemorrhage, and liver transplantation. The definition of massive blood transfusion has evolved over time. In the 1970s, massive transfusion was defined as more than 10 units of blood over a 24-hour period. This is equivalent to approximately one patient blood volume in a person of average weight person.⁴ Recent reviews in the literature have expanded this definition, with some reports using up to 50 units of blood in 24 or 48 hours.³

As technology and blood banking procedures have improved, patient outcomes following transfusion have also improved. Review of the literature for massive transfusion dates back to the 1960s. Reported survival rates for patients receiving 10 units of blood in 24 hours were dismal (6.6%).⁴ However, in recent years, patient outcome has improved, with survival rates of up to 60%⁵⁻¹⁰ in patients requiring much more significant transfusions, i.e., >50 units of blood in the early resuscitation period (Table 2).

In 1987, Phillips et al⁵ reported on 56 patients who received massive transfusion exceeding two times their blood volume (>20 units within 24 hours). Overall survival was 39% and all 22 survivors had penetrating trauma. Of the nonsurvivors, 21 had penetrating trauma, 6 had blunt trauma, and 7 were nontraumatic surgical emergencies.

In 1991, Wudel and colleagues⁶ reported massive transfusion outcomes in patients with blunt trauma. Again, these patients received more than 20 units (range, 20-126) of packed red blood cells during their hospitalization. Of the 92 patients with blunt

Table 2. Review of Survival Statistics in Massive Transfusion

Study/Year	No. of Patients	Transfusion Volume (units)	Overall Survival (%)
Phillips et al ⁵ 1987	56	35.3	9
Wudel et al ⁶ 1991	92	20 (20-126)	52
Harvey et al ⁷ 1995	43	19.2	60
Velmahos et al ⁸ 1998	141	31.5	31
Cinat et al ⁹ 1999	46	63.1	45
Vaslef et al ¹⁰ 2002	44	>50	43

trauma, 48 (52%) survived and were discharged from the hospital. Not all the transfused blood was given within the first 24 hours of admission. Specifically, 82% was administered in the first 24 hours, 5.5% during the second 24 hours, and 12.5% more than 48 hours after admission. This report also addressed long-term follow-up to 2.5 years. Of the 48 patients, 5 patients were lost to follow-up, but 32 patients (74.4%) returned to gainful employment.

In 1999, Cinat et al⁹ performed a retrospective review of 46 trauma patients who were hospitalized between 1988 and 1997 and who received more than 50 units of packed red blood cells or whole blood within 48 hours of arrival at the emergency department. These patients were divided into early (1988-1992) and late (1993-1997) periods for comparison. The results demonstrated a significant increase in survival over the 10-year period studied (16% vs. 45%, early vs. late period, $P = .03$). Factors affecting adverse outcomes included male sex, major vascular injury, high Injury Severity Score, severe acidosis, prolonged hypotension, refractory hypothermia, and decreased use of platelet transfusion (all $P < .05$). In the later period, survival was improved as the result of more aggressive correction of *coagulopathy*, more effective and efficient rewarming procedures, improved application of damage control techniques, and increased use of component therapy resulting from improved blood banking procedures (all $P < .05$). More recent reviews support this rate of survival in trauma patients who receive over 50 units of blood products in the first 24 hours¹⁰ (Table 2).

Complications of Massive Transfusion

The aim of treatment of massive blood transfusion is not only to restore adequate blood volume, but to also support hemostasis, maintain oxygen-carrying capacity, and restore or maintain oncotic pressure. Although survival has improved, massive transfusion can be associated with many complications and side effects. Physicians caring for patients that require massive transfusion must anticipate, identify, and rapidly treat these potential complications early to ensure optimal patient outcome.¹¹

Dilutional thrombocytopenia is inevitable following massive blood transfusion. This results from a decline in platelet function with the storage of blood after only a few days. Typically, 1.5 times the normal blood volume must be transfused for dilutional thrombocytopenia to occur, but there are reports of cases with smaller volumes of transfusion, especially if there is associated disseminated intravascular coagulation or preexisting thrombocytopenia.

Disordered hemostasis is also a known complication of massive blood transfusion attributed to lack of factors V and VIII in stored blood. Oxygen delivery is also affected because of the high oxygen affinity of stored blood. Longer storage periods lead to a reduction in red cell deformability, altered red cell adhesiveness, and other red

cell storage lesions. These changes reduce red blood cell viability after transfusion, reduce tissue oxygen availability, and promote proinflammatory and immunomodulatory effects, specifically neutrophil priming and pulmonary endothelial cell activation.

Systemic inflammation and potential tissue injury may also be induced by the transfusion of aged blood. Zallen et al¹² showed that transfusion of blood older than 14 days in the first 6 hours of resuscitation is an independent risk factor for postinjury multiorgan failure. This may be particularly significant in large trauma centers and transplantation centers where older blood is preferentially distributed because of their high-volume use. Until further data are available, the use of relatively fresh blood products (<1 week old) seems prudent.

Blood transfusion is a form of temporary transplantation. In a recipient who is immunocompetent this can result in an immune response to the donor antigens known as alloimmunization. The antigens most often involved include HLA class I and II on platelets and leukocytes, granulocyte-specific antigens, platelet-specific antigens, and red blood cell-specific antigens. Consequences of alloimmunization include a refractory response to platelet transfusion, posttransfusion purpura, neonatal alloimmune thrombocytopenia, acute intravascular hemolytic transfusion reaction, hemolytic disease in newborns, and febrile nonhemolytic reactions against granulocytes. Clinical manifestations can be minor, such as fever, or fatal, leading to active bleeding and hemolysis. Workup and treatment are also varied, depending on the severity of reaction.¹³

Citrate toxicity can occur in patients with abnormal liver function or in whom the administration of blood is very rapid. The healthy adult liver will metabolize 3 g of citrate every 5 minutes. Each unit of blood contains approximately 3 g of citrate. Therefore, transfusion rates higher than 1 unit every 5 minutes can exceed the liver's capacity to handle such large amounts of citrate. The citrate then binds calcium and can lead to clinical hypocalcemia. Patients may exhibit temporary tetany and hypotension.

Electrolyte disturbances such as hyperkalemia or hypokalemia can occur. The longer the shelf life of blood, the higher the potassium concentration; sometimes concentrations may even exceed 30 mmol/L. Unless very large amounts of blood are transfused, hyperkalemia is generally not a problem. On the other hand, as red cells begin active metabolism, intracellular uptake of potassium begins and hypokalemia can occur.

Acid-base disturbances can also occur with massive blood transfusions. Stored blood contains lactate at levels up to 30 to 40 mmol/L. In addition, citric acid is present and may be metabolized to bicarbonate, resulting in severe metabolic alkalosis. Conversely, the patient's overall condition and tissue hypoperfusion may actually lead to metabolic acidosis.

Transfusion-related acute lung injury (TRALI) is a devastating complication of massive transfusion and consists of a syndrome that includes dyspnea, hypotension, bilateral pulmonary edema, and fever. Its incidence is reported to be between 0.04% and 0.06% (or approximately 1 in 2,000). Clinically, it resembles adult respiratory distress syndrome. The proposed cause has been linked to immune mechanisms, specifically HLA antibodies and granulocyte antibodies in stored blood components, which form immune complexes.¹⁴ These immune complexes are deposited in the pulmonary vascular bed and release vasoactive substances, causing leakage of fluid into alveolar spaces, activation of complement, leukostasis, and activation of polymorphonuclear neutrophils.¹⁵ Treatment is generally supportive and includes ventilatory and hemodynamic assistance. There are no data to support the use of corticosteroids, and additional blood component therapy should be given if clear transfusion needs exist.¹⁶

Blood transfusion can also result in induction of acquired inhibitors of coagulation. The most common antibodies are directed against coagulation factor VIII. This can result in massive bleeding,

which is difficult and costly to treat. The main goals of treatment are to stop the hemorrhage and remove the inhibitor. Factor VIII concentrate is used only for life-threatening circumstances. Successful elimination of anti-VIII has been accomplished with the use of oral immunosuppressants such as cyclophosphamide and prednisone.¹⁷

Massive transfusion can also be associated with hypothermia if blood products are not appropriately warmed during transfusion. Hypothermia causes decreased lactate and citrate metabolism, leading to hypocalcemia and metabolic acidosis, increased hemoglobin affinity for oxygen, altered red cell deformability, platelet dysfunction, and cardiac conduction abnormalities. Both undertransfusion and overtransfusion can be associated with acute respiratory distress syndrome, although the exact pathophysiology is not known.

Role of Recombinant Factor VIIa in Massive Transfusion

Newer developments in transfusion therapy include the discovery and use of coagulation factor VIIa (recombinant). This is a synthesized analog of human factor VII. Recombinant factor VIIa (rFVIIa) has been used effectively in the treatment of patients with hemophilia as well as other congenital and acquired coagulopathies. There have been reports recently of the successful use of rFVIIa in treating coagulopathic trauma patients.¹⁸ Patients with active hemorrhage and clinical coagulopathy from diverse causes such as traumatic hemorrhage, traumatic brain injury, warfarin use, congenital factor VII deficiency, and other acquired hematologic defects were administered rFVIIa as a last resort. Coagulopathy was reversed in 75% of patients, with an associated decrease in protime. Forty-two percent of patients survived to hospital discharge.

Recently, two randomized prospective placebo-controlled, double-blind trials were conducted simultaneously to evaluate the efficacy and safety of recombinant factor VIIa as adjunctive therapy for the control of bleeding in patients with severe blunt (n = 143) or penetrating (n = 134) trauma. In blunt trauma, the red blood cell transfusion requirement was significantly reduced by 2.6 units ($P = .02$), and the need for massive transfusion (>20 units of packed red blood cells) was reduced (14% vs. 33%, $P = .03$). In patients with penetrating trauma, the trends were similar, but not significant (reduction in red cell transfusion of 1.0 unit, $P = .10$; massive transfusion 7% vs. 19%, $P = .08$). Trends toward reduction in mortality and critical complications were also observed. Further studies need to be done to clearly evaluate the efficacy, safety, and cost-effectiveness of recombinant factor VIIa in the management of trauma patients.¹⁹

Massive Transfusion Protocols

When massive transfusion is contemplated, a protocol should be instituted. There are many variations of a Massive Transfusion Protocol (MTP), but the basic components are the same. The following is an example of a MTP from the State Trauma Advisory Board Management Recommendation.²⁰ Initiation of MTP is the responsibility of the attending physician. Key participants include the attending physician, the trauma nurse, the blood bank technologist, and, potentially, the anesthesiologist. The blood bank, Red Cross, and on-call pathologist are notified. Blood is drawn for ABO, Rh type, antibody screen, arterial blood gas, electrolytes, hematocrit, and coagulation panel including protime, partial thromboplastin time, fibrinogen, and platelets. Massive transfusion packs are provided by the blood bank. The composition of this pack can vary from institution to institution. At our institution, the composition of this pack includes 8 units of packed red blood cells, 2 units of fresh-frozen plasma, and 1 platelet pheresis. This pack is automatically refilled continuously until ordered to be discontinued

by the attending physician. Additional blood components can be ordered as needed, based on the patient's coagulation profile or clinical presentation. Patients will be transfused with type-specific or cross-matched blood whenever possible. Uncross-matched blood may be used in emergencies. The nurse is responsible for contact between the blood bank and delivery of blood products to the patient's location. Hemodynamics and further laboratory evaluations are also performed by the nurse. The attending physician has the primary responsibility for correcting hypothermia, electrolyte, osmolar, and acid-base disturbances. The medical director of the blood bank is responsible for follow-up of all massive transfusion cases. The attending physician will slow and/or terminate the MTP based on clinical and laboratory evidence of improvement in bleeding and coagulation.

Conclusion

In review, the science of transfusing blood has greatly advanced and has led to successful outcomes in patient requiring massive transfusion. Early reported survival rates were dismal (6.6%),⁴ but recently the survival rate for trauma patients following massive transfusion has improved to 45% to 60%.⁵⁻¹⁰ Recent literature also demonstrates no survival difference in patients with blunt versus penetrating trauma. Improved survival has been attributed to improvement in trauma care provision, particularly in increased attention to rewarming during the resuscitation of hypothermic patients, damage control celiotomy to improve control of hemorrhage, identification of injuries, and control of contamination. In addition, transfusion practices have changed to include more aggressive transfusion with platelets and fresh-frozen plasma. Therefore, massive transfusion is not futile in trauma patients, and good outcomes can be achieved. Massive transfusion for trauma is appropriate.

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Blood Transfusion and Outcomes Research

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Learning Objectives: 1) To learn of the contemporary risks of blood transfusion. 2) To understand that no prospective randomized trials were involved with the development of blood transfusion. 3) To appreciate that contemporary outcomes research has shown that patients receiving blood transfusion have worse outcomes compared with those who receive less blood. The only relative large randomized trial shows that patients receiving more blood did worse or no better than those who were transfused less. Other smaller randomized trials have not shown any advantage to transfusion.

Abstract

Modern blood banking is approximately 105 years old, dating back to the first description of the ABO-rH system. Since that time no prospective trials of efficacy of blood transfusion have been mandated as they would for the approval of a new drug. The only trials that exist show that either blood transfusion makes no difference to outcome or that in some subgroups of patients it is linked with a higher death rate than in those patients receiving less blood. Data-based research cannot prove cause-and-effect, but a consistent finding is the association of blood transfusion to more infection, immunosuppression, longer hospital stays, more multisystem organ failure, transfusion-related acute lung injury, and other dysfunctions. Clearly, an appropriate or best practice for blood transfusion must exist. In massive blood loss cases, transfusion surely saves lives. A lot of research is yet to be conducted in many different subgroups of patients before we have a clear guidance for the practitioner for when it is best to transfuse.

Transfusion of allogeneic blood is now 105 years old in the modern era. Its use grew throughout the 20th century, with major changes in practice surrounding the conflicts of the First and Second World Wars.¹ Blood banking has focused on supply as a major problem. Indeed, supply continues to be one of the biggest challenges facing the blood banking industry today.² Shortages of stored red cell products in the United States may approach 10% to 15% this year alone, and regional short-term crises result when blood is not available.³ Costs of blood products are rising faster than other medical care costs. It is expected that a unit of red blood cells may cost more than \$500.00 in the next 3 to 5 years. The United States Congress is aware of these critical issues, as are the organizations governing the collection and distribution of blood.

In the 1970s it became widely known that allogeneic blood transfusion carried a high risk of viral disease transmission.^{1,3} Hepatitis C (at that time known as non-A, non-B) was present in about 1% of all units transfused, but because of the relatively large number of units that each transfused patient received, the risk of seroconverting after transfusion was widely quoted to be at 10%. The prevailing transfusion practice did not ever question whether transfusion improved patient outcome. It was simply accepted that blood transfusion was good, and the risk of hepatitis was therefore accepted. When the acquired immunodeficiency (AIDS) crisis was felt in the Western World, the lay press focused on viral disease transmission in the blood supply. With such public pressure the medical profession refocused their thinking and began a number of safety steps to reduce viral transmission. Not only were donor criteria made stringent and paid donors outlawed, eventually nucleic acid testing for portions of viral DNA led to very effective detection of possible infectious units. Today, the scourge of hepatitis and AIDS has been almost eliminated from the blood supply. The risk of contracting hepatitis C is probably in excess of 1/1,000,000 units transfused, and the risk of contracting AIDS is approximately 1/1.5-2.5 million units transfused. Hepatitis B may be more common at approximately 1/150,000-500,000 units transfused.^{4,5}

In the 1970s a national study followed more than 300,000 patients who had contracted hepatitis through blood transfusion.⁶ Approximately 1,000 of these patients died every year, and many others developed chronic active hepatitis leading to cirrhosis and hepatomas. No researcher in that very large National Institutes of Health-sponsored series of studies asked the important question if the medical profession knew whether transfusion was improving outcome.

Although today we have largely defeated the risks of hepatitis and AIDS from blood transfusion, the laymen still focus on these viral pathogens. It is the responsibility of the medical community to shift public opinion and understanding to contemporary appropriate risks and outcomes from transfusion. Modern blood banking tests only for certain viruses, but many more are present in most transfusions. Transfusion-transmitted virus is present in a significant number of units tested (8-82%).⁷⁻¹⁰ Debate continues as to whether