Massive blood transfusion therapy

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1999 Student Writing Contest Winner

Surgical patients requiring massive blood transfusion therapy present many challenges for the anesthetist. The decision to transfuse homologous banked blood and its components must be weighed against the potential complications that may occur in this form of therapy. A review of metabolic changes that occur in banked blood, the risk of infection, and physiologic derangements that may develop during massive blood transfusion are presented.

Key words: Coagulopathies, massive blood transfusions.

Introduction

Massive transfusion may be defined as replacement of a patient's entire estimated blood volume within 24 hours or replacing 50% of the estimated blood volume within 3 hours or less. It also may be defined as the administration of more than 10 units of whole blood or more than 20 units of packed red blood cells.[1] This article explores the implications and complications associated with transfusing multiple units of blood.

Review of literature

Many structural and metabolic changes occur in banked blood that affect the viability and function of red blood cells. Red blood cell storage results in a depletion of 2,3-diphosphoglycerate (2,3-DPG).[1] 2,3-DPG is a molecule that reduces the affinity of hemoglobin for oxygen, thus allowing oxygen to be released to the tissues and causing a rightward shift of the oxyhemoglobin dissociation curve. Because stored red blood cells consume glucose and, therefore, produce lactic acid through glycolysis, the pH of the unit decreases during storage. The acidity created by the preservative solution and lactic acid production interferes with the enzyme activity necessary for continued synthesis of 2,3-DPG.[2]

Red blood cells become spherical and irregularly shaped due to hemolysis and shedding of the lipid membrane. Microaggregates, such as platelets, leukocytes, and small fibrin clots, accumulate with storage and may not be filtered with the standard 170-μm blood filter.[2] Some suggest using a micropore filter to prevent respiratory sequelae in severe trauma or hemorrhage and for patients with adult respiratory distress syndrome since these particles lead to vascular obstruction in the lungs.[3]

Banked blood is subject to aberrations in electrolyte availability and values. Citrate is added to the preservative fluid of red blood cells because of its anticoagulant effect and to preserve 2,3-DPG. Once in the body, citrate binds to calcium, and ionized calcium levels decrease. Hypocalcemia develops with massive blood transfusions because the citrate preservative in blood binds to calcium in the body. In healthy people, when the transfusion is stopped, the liver immediately begins to metabolize citrate. In liver disease and

hypothermia, the rate of metabolism can decrease profoundly.[3] Hypocalcemia can manifest as hypotension, prolonged QT interval, and increased left ventricular end-diastolic, pulmonary artery, and central venous pressures. Administration of calcium chloride is the preferred treatment of hypocalcemia because it contains 3 times the amount of calcium compared with calcium gluconate.[3] Citrate intoxication has been reported as occurring fewer than 5 minutes following administration of a unit of blood.

Potassium levels increase, especially after a month of storage. For example, on the day blood is obtained, the potassium level is usually about 3.3 mEq/L (3.3 mmol/L), and on day 35, it can be as high as 17.2 mEq/L (17.2 mmol/L). This is due to the inactivation of the sodium-potassium pump by the cold temperatures required for preservation and storage.[4]

After 2 days of storage, blood is devoid of platelets.[2] This is because refrigeration causes oxidation and death of viable platelets.[5] Most coagulation factors remain relatively stable with the exception of factors V and VIII. Factor VIII is part of the intrinsic coagulation pathway and a cofactor in developing factor X.[2] Factor X is required to activate factor V, which initiates the cascade to develop a fibrin clot.[4]

Although only 5% to 20% of factor V and up to 30% of factor VIII is required for normal homeostasis, thrombocytopenia from dilution still occurs frequently during massive transfusion.[5] If patients receive aggressive fluid administration before blood transfusion, a dilution of clotting factors occurs and bleeding increases. Consequently, microvascular bleeding can result, requiring replacement of platelets and coagulation factors.

The coagulation system is in balance preventing excessive clotting or excessive bleeding. Normal hemostasis consists of 2 steps, primary and secondary hemostasis. Primary hemostasis occurs when circulating platelets recognize endothelial injury and begin to form a platelet plug. If the injury is large, secondary hemostasis is then activated.[5,6]

Secondary hemostasis begins when a fibrin clot is formed to reinforce the platelet plug. This fibrin clot is activated by the intrinsic or the extrinsic pathway.[4] A precursor of the intrinsic pathway is the binding of subendothelial collagen and factor VIII, which circulates in the plasma. The extrinsic pathway is stimulated by thromboplastin, which is released by the injured endothelial cells. Thrombin is produced by the platelet plug-fibrin clot, which converts fibrinogen to fibrin, creating a stronger clot.[5,6]

The fibrinolytic system is activated to preserve the liquidity of blood once hemostasis has begun. In response to thrombin, protein plasminogen is excreted from the clot to form plasmin. Plasmin then will destroy fibrin products and coagulation factors. This process ensures balance in the overall function of the hemostatic system.[5,6]

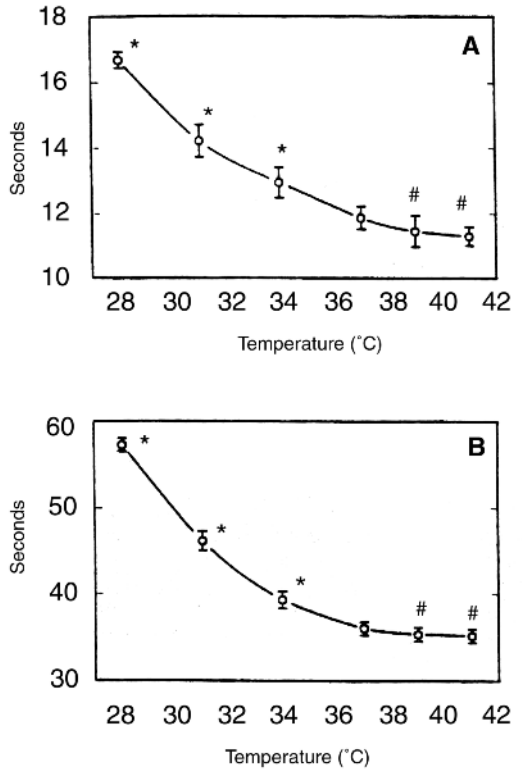
Administering fresh frozen plasma routinely to patients receiving massive blood transfusions is unnecessary and wasteful.[2] Cookbook recipes for administering platelets and fresh frozen plasma should be avoided. The administration of these blood products should be based on clinical evidence, such as bleeding and laboratory analysis of prothrombin time and partial thromboplastin time values.

Hypothermia becomes a significant challenge during massive transfusion. Transfusing multiple units of blood products and the presence of shock can compound this problem. There is a relationship between the number of units transfused and the degree of hypothermia. More significant is the relationship between hypothermia and microvascular bleeding. There is an approximate linear relationship among temperature, prothrombin time, and partial thromboplastin time (Figure).[7] Hypothermia prolongs prothrombin time and partial thromboplastin time.

Several studies indicate that hypothermia inhibits the enzymes necessary to initiate the coagulation cascade and formation of clotting factors.[8-10] A critical point is reached at 34˚C that results in significant reductions in platelet activity.[9] Frequently, blood obtained intraoperatively is warmed by the laboratory and calculated at 37˚C and not at the patient's body temperature.[11] Commonly, the coagulation tests performed intraoperatively are performed at 37˚C and not at the patient's body temperature. These tests can underestimate the severity of coagulopathies. Adequate coagulation during massive transfusion requires judicious replacement of clotting factors and use of rewarming techniques.

The shock state of the patient may have more influence than the implications of massive transfusions on patient outcomes.[12] In a study by Velmahos et al,[10] the longer the time with a systolic blood pressure less than 90 mm Hg and the longer the duration of shock, the more likely the patient would die regardless of the number of units transfused. Factors identified that increase the probability of death include aortic clamping, increased age, intraoperative use of inotropic drugs, systolic blood pressure less than 90 mm Hg, and a temperature less than 34°C.[12]

Figure. **The effect of temperature on prothrombin time (A) and activated partial thromboplastin time (B) determinations**



* $P < .001$ when compared with the mean at 37°C, or any other temperature; # $P < .01$ when compared with the mean at 37°C.

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Transmission of blood-borne pathogens is an additional risk when administering blood products. The potential for transmission is multiplied by the total number of units transfused. The risk of transmitting human immunodeficiency virus (HIV) to a recipient has been reported to be 1:360,000[13] to 1:493,000[14] transfusions. HIV may be present but undetected by current technology available for screening. Obtaining blood during the window period of 24 to 35 days after infection may result in a false-negative result.[13,14] This risk, however, has decreased during the last few years as a result of recruitment of low-risk donors, improvement in the interview process, and increased sensitivity of HIV testing.[14]

The risk of transmitting hepatitis is higher than that for HIV because of the longer window period (37 to 192 days) for hepatitis.[14] Studies indicate that the risk for transmission of hepatitis C virus is 1:103,000 and for hepatitis B virus, is 1:63,000 transfusions.[15] Seroconversion rates are higher for hepatitis B virus than for hepatitis C virus, 9.8:100,000 and 4.32:100,000 respectively.[15] Approximately 10% to 20% of infected hepatitis C virus recipients will develop liver disease. Those infected with hepatitis B virus are at risk of developing acute hepatitis.

Fatal hemolytic reactions occur due to the incompatibility of the donor's red blood cell antigen with the recipient's serum antibody.[2] Renal failure can result due to deposition of red blood cell debris and thrombi in the renal vasculature. Key signs and symptoms are masked by anesthesia. The only symptoms identifiable are unexplained hypotension, significant hemoglobinemia, and active bleeding at the surgical site. The risk of this reaction is reported as 1:33,000 to 1:100,000 transfusions. Research shows that 59% of these reactions occur in the operating room and involve patients with type O blood 49% of the time.[16] The majority are due to a clerical error involving same last names and removal of the patient's identification band.[15] In an emergency, for example, losing more than 40% of total blood volume, type O blood can be administered without typing or crossmatching.[2] However, this is not without consequence. Type O blood must be used thereafter to avoid hemolysis from the increased levels of anti-A and anti-B titers. If blood is needed before compatibility testing, obtain ABO-Rh typing and crossmatch immediately, which usually takes 5 minutes.[2] Another option is to administer uncrossmatched, type-specific blood.

Nonhemolytic reactions may occur in patients who have received a previous transfusion. Also, women with a history of multiparity may become sensitized to red blood cell antigens during their pregnancy.[2] If they receive a blood transfusion in the future, these antibodies may react with the donor's leukocytes and platelet antigens. The only sign identifiable under anesthesia may be a high fever.[2]

Discussion

More then one half of blood given to patients in the United States is given in the operating room.[2] Each institution has practice guidelines, but it is imperative to understand the indications of specific blood components as applied to each patient. The American Society of Anesthesiologists (ASA) Task Force on Blood Component Therapy released a report in 1996 on practice guidelines and recommendations.[17] Overall, the ASA suggested that the decision to transfuse should be based on the risks of developing complications

from inadequate provision of oxygen rather than on a single trigger, such as a specific hemoglobin value. These guidelines include the following:

1. Infrequent is the need for red blood cell transfusion if the hemoglobin is more than 10 g/dL (100 g/L) and most often is indicated when hemoglobin is less than 6 g/dL (60 g/L).[17]

2. Platelet transfusion is based on the risk of bleeding if platelets counts are between 50 and 100 × 10^3/μL (50 and 100 × 10^9/L) and usually is appropriate for surgical patients with levels less than 50 × 10^3/μL (50 × 10^9/L).[3,17]

3. Fresh frozen plasma is indicated for reversal of warfarin therapy, known coagulation deficiencies, or microvascular bleeding with prolonged coagulation laboratory values or in the absence of values when more than 1 unit of blood is transfused.[17]

4. Cryoprecipitate is indicated as prophylaxis for von Willebrand disease, to treat active bleeding in von Willebrand disease, or for patients receiving massive blood transfusions.[17]

The American College of Surgeons Committee on Trauma developed Advanced Trauma Life Support guidelines for fluid and blood requirements. This algorithm is divided into 4 classes of presentation and is based on estimated blood loss, vital signs, capillary blanch test, urine output, and mental status.[2] Combining these recommendations with the ASA's guidelines can provide sound rationale for blood administration.

Summary

The ability to transfuse blood with relatively few complications has led to increased survival for patients requiring massive amounts of blood. Overall, the indications for transfusing blood products need to be based on the entire clinical picture that is specific for each patient.[16] The response of patients to massive blood transfusions can clearly be magnified by preexisting disease. A knowledgeable approach includes attention to a scientific framework for practice and consideration of consensus-panel practice guidelines, including local practice patterns. This is key to the rational therapy of patients requiring massive blood transfusion.

REFERENCES

(1) Fakhry SM, Messick WJ, Sheldon GF. Metabolic effects of massive transfusion. In: Rossi EC, ed. *Principles of Transfusion Medicine.* 2nd ed. Baltimore, Md: Williams & Wilkins; 1996:615-625.

(2) Bernstein DP. Transfusion therapy in trauma. In: Capan LM, Miller SM, Turndorf H, eds. *Trauma: Anesth Intensive Care.* Philadelphia: JB Lippincott Co; 1991:167-205.

(3) Miller RD. Transfusion therapy. In: Miller RD, ed. *Anesthesia*. 4th ed. New York, NY: Churchill Livingstone; 1994:1619-1646.

(4) American Association of Blood Banks. Blood and components. In: *AABB Technical Manual.* 12th ed. Bethesda, Md: American Association of Blood Banks; 1996:135-156.

(5) Czinn EA, Chediak JR. Coagulation and hemostasis. In: Salem MR, ed. *Blood: Conservation in the Surgical Patient*. Baltimore, Md: Williams & Wilkins; 1996:45-78.

(6) Morgan GE, Mikhail MS. Hepatic physiology and anesthesia. In: Morgan GE, Mikhail MS, eds. *Clinical Anesthesiology*. 2nd ed. Stamford, Conn: Appleton & Lange; 1996:611-624.

(7) Rohrer MJ, Natale AM. Effect of hypothermia on the coagulation cascade. *Crit Care Med.* 1992;20:1402-1405.

(8) Watts DD, Trask A, Soeken K, Perdue P, Dols S, Kaufmann C. Hypothermic coagulopathy in trauma: effect of varying levels of hypothermia on enzyme speed, platelet function, and fibrinolytic activity. *J Trauma.* 1998;44:846-854.

(9) Wilde JT. Hematological consequences of profound hypothermic circulatory arrest and aortic dissection. *J Card Surg.* 1997;12:201-206.

(10) Velmahos GC, Chan L, Chan M, et al. Is there a limit to massive blood transfusion after severe trauma? *Arch Surg.* 1998;133:947-952.

(11) Reed RL, Johnson TD, Hudson JD, Fischer RP. The disparity between hypothermic coagulopathy and clotting studies. *J Trauma.* 1992;33:465-470.

(12) Gubler KD, Gentilello LM, Hassantash SA, Maier RV. The impact of hypothermia on dilutional coagulopathy. *J Trauma*. 1994;36:847-851.

(13) Lewis F, Notari EP, Petersen LR. Estimated risk of transmission of the human immunodeficiency virus by screened blood in the United States. *N Engl J Med.* 1995;333:1721-1725.

(14) Schreiber GB, Busch MP, Kleinman SH, Korelitz JJ. The risk of transfusion-transmitted viral infections. *N Engl J Med*. 1996;334:1685-1690.

(15) Sazama K. Reports of 355 transfusion-associated deaths: 1976-1985. *Transfusion.* 1990;30:583-590.

(16) Greenburg G. New transfusion strategies. *Am J Surg.* 1997;173:49-52.

(17) American Society of Anesthesiologists. Practice guidelines for blood component therapy. *Anesthesiology.* 1996;84:732-747.

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