Perioperative blood transfusion: a brief review of pros and cons

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Abstract

In the treatment of anemia, potential benefits should be weighed against risks, costs and limited availability of blood products. Alternatives to blood transfusion, such as preoperative blood donation and pharmacological interventions (e.g., erythropoietin, intravenous iron supplementation, etc.) ought to be considered before deciding on blood transfusion for the correction of anemia. In normovolemic patients with adequate cardiopulmonary function, acute anemia is usually tolerated well. Therefore, acute normovolemic hemodilution, eventually combined with preoperative autologous blood donation, and/or intraoperative red cell salvage, may reduce the requirements of perioperative transfusion of homologous blood.

A universal threshold of hemoglobin level for blood transfusion has not been established. Patients with co-existing diseases (especially cardiopulmonary pathologies) may potentially benefit from a higher hemoglobin level. However, there is no clear-cut data-based evidence to support the necessity of a higher hemoglobin level transfusion threshold in these patients.

Transfusion of blood products is associated with risks, some of them life threatening; therefore, the indication for transfusion should be weighed individually, based on a risk-benefit ratio consideration. Nevertheless, in clinical practice, surgeons and anesthesiologists are liberal in prescribing blood products.

The purpose of this brief review is to draw the readers’ awareness to the potential danger associated with blood transfusion and discuss existing alternative means of counteracting acute perioperative anemia.

Keywords: transfusion: blood products, indications, complications, alternatives to blood transfusion

Introduction

The practice of transfusion medicine has undergone substantial change over the last decade. Much of the impetus for the change has come from isolation of human immunodeficiency virus (HIV) and the linkage of HIV transmission to blood transfusion. Surgical patients often lose blood and receive red blood cell (RBC) transfusion to restore normal oxygen transport and delivery to the tissue. In United States, around 14 million units of RBC are collected and about 11 million units are transfused to 3.4 million patients annually [1]. It is estimated that approximately 60-70% of these units are transfused in the perioperative period [2]. The paucity of evidence regarding blood transfusion in surgical patients led to controversies concerning indications for perioperative blood transfusion. While the potential risks associated with blood transfusion are well described, much less is known about its benefits [3].

Former surgical and anesthetic practice guidelines were based on the belief that at hemoglobin (Hb) values of less than 10 g/dL, or hematocrit < 30%, oxygen availability to the tissues and organs is impaired. For a
long time it was widely accepted that no patient should be subjected to elective surgery unless his/her preoperative hemoglobin concentration was 10 g/dL [4]. However, the American Society of Anesthesiologists (ASA) guidelines [3] have recommended maintaining perioperative Hb levels higher than 6-8 g/dL, whereas the National Institute of Health considers a hemoglobin concentration > 7 g/dL acceptable, depending on the patient’s physical status and co-existing diseases [5]. Despite these guidelines, and the risks of blood transfusion (see below), surgeons and anesthesiologists are often liberal and frequently inconsistent in prescribing transfusion of blood and blood products in the perioperative period. In the setting of cesarean delivery, Matot et al evaluated the Israeli anesthesiologists’ and gynecologists’ attitude toward clinical practice of blood administration. The survey showed a very heterogeneous policy, emphasizing that none of these groups adhered to the currently accepted transfusion protocols [6].

This review aims at briefly summarizing the concept of blood rheology and oxygen delivery, the pathophysiology of acute anemia, the morbidity associated with perioperative blood transfusion, alternative strategies to allogeneic blood transfusion and finally it outline the appropriate modes of perioperative blood component utilization, while following the current transfusion guidelines.

**Blood rheology and oxygen delivery to the tissues**

Tissue oxygen delivery (DO2) is the product of blood flow and arterial oxygen content (CaO2). O2 delivery is the product of total blood flow, or cardiac output (CO), and arterial O2 content. Blood flow is determined by the resistance to flow in the vascular bed and the perfusion pressure driving the flow through it. Resistance to flow is related linearly to the length of the vessels and inversely to the fourth power of the radii of the vessels (Poiseuille’s law). Reduction in hematocrit decreases blood viscosity and the shearing force required to maintain flow at any given shear rate. This occurs more prominently in the microcirculatory system where low shear rates exist [7]. The increased tissue blood flow that results from the lower viscosity must be sufficient to compensate for the lower oxygen carrying capacity and to preserve tissue oxygen delivery (DO2) [7]. Nevertheless, intraoperative blood loss is not immediately compensated for with red blood cell transfusion. Shed blood is first replaced by crystalloids (3:1) and/or colloidal (1:1) infusion solutions. With increasing dilution of circulating red blood cell mass, the Hb concentration, the hematocrit (Htc) and the arterial oxygen content (CaO2), decrease exponentially. Normovolemic hemodilution may lead to beneficial rheological properties, e.g., better passage of RBCs in the microcirculation [8]. As a consequence, improved microcirculation augments venous return and cardiac output, mainly by increasing the stroke volume, heart rate and decrease in vascular resistance [9].

**Pathophysiology of acute anemia**

Anemia is defined as a reduction in red blood mass of 10% or more, usually manifested by a decrease in blood Hb. The physiologic aspects of anemia were thoroughly described in a comprehensive review by Hébert et al [7].

Blood has an oxygen-carrying capacity of 1.34 ml of oxygen per 1 gram of hemoglobin; thus, at a hemoglobin of 15 g/dL, one liter of blood carries about 200 ml of oxygen. The heart, specially the left ventricle, may be sensitive to the adverse consequences of anemia, because the myocardium consumes 60%-75% of all oxygen delivery to the coronary circulation. As a result, the oxygen delivery to the myocardium primarily increases by increasing blood flow. Below a hematocrit (Htc) value of 25%, the cardiac output compensation for dilutional anemia becomes exhausted and the DO2 starts to decrease, but tissue oxygen consumption (VO2) remains still unchanged despite the falling DO2. When O2 availability becomes limited, the VO2 becomes more dependent upon DO2, thus, indirectly indicating the onset of tissue hypoxia. This point is called “critical DO2”. The Htc value that corresponds to the critical DO2 is called “critical hematocrit” and reflects the physiologic limit of dilutional anemia. Perioperative factors that influence the critical O2 delivery include blood volume, depth of anesthesia, degree of muscle relaxation, body temperature, inspiratory oxygen fraction (FiO2), and myocardial performance [7].

A study in healthy humans showed that acute normovolemic hemodilution to 5 g/dL hemoglobin was well tolerated without signs of tissue hypoxia [9]. Several case series reports of patients, such as Jehovah’s Witnesses, who refused blood transfusion, demonstrated that during major surgery, Hb levels < 10 g/dL are well tolerated without an apparent increase in major morbidity or mortality [10, 11].

Numerous studies have evaluated the effect of RBC transfusion on oxygen kinetics. Oxygen delivery uniformly increased, but a change in oxygen consumption was observed in only few studies. Therefore, there is no consensus in regard to which patients are most likely to benefit from blood transfusion and which intervention or approach is superior (i.e. administration of fluids, blood transfusion, inotropic agents or a
combination of them) in improving oxygen tissue delivery [7].

Despite the evidence that low hemoglobin values (anemia) are generally well tolerated, surgeons and anesthesiologists continue to “stick” to rigid transfusion thresholds. In a survey among Canadian anesthesiologists, there was a significant variation in transfusion practices. The type of surgical procedure, patient’s age and a history of coronary artery disease influenced reported transfusion threshold. Other factors that influenced the decision to transfuse specifically in patients with coronary artery disease undergoing coronary artery bypass surgery were older age, the presence of myocardial ischemia and low cardiac index. Practice variations in specific subgroups would support the need for further research to identify optimal transfusion thresholds [12].

Treating anemia with blood transfusion may increase the hemoglobin to a specific target level but this correction may be on account of some deleterious complications associated with blood transfusion.

**Morbidity associated with blood transfusion in the perioperative period**

Adverse events (morbidity) associated with blood transfusion, which occur immediately before, during or after surgery, include, but are not limited to, the risk of transmission of infectious diseases, transfusion-associated immune-modulation, cardiovascular complications, increased risk of perioperative infections, transfusion related acute lung injury (TRALI), transfusion blood group reactions, graft-versus-host reactions, and others [13].

This brief review will deal with only a few of the well-known transfusion-related complications.

**Transmission of infectious diseases**

Blood transfusion in Western countries is considered relatively safe with respect to transfusion-transmissible viruses, such as human immunodeficiency virus (HIV), hepatitis B (HBV), hepatitis C (HCV), hepatitis D, hepatitis G and Epstein-Barr (EBV) viruses. Bacterial infections with Treponema pallidum, Yersinia enterocolitica, and parasites such as Plasmodium species, Trypanosoma cruzi (Chagas’ disease) and Babesia microti, are also rarely transmitted nowadays by blood transfusion, as it is also the case with the Creutzfeldt-Jacob disease [14].

**Recurrence of cancer**

The majority of the noninfectious adverse events of blood transfusion are immune-mediated. Observational studies have suggested the existence of a linkage between allogeneic RBCs administration and recurrence of cancer. It has been hypothesized that allogeneic blood transfusion depresses the immune function, thereby promoting tumor growth in oncology patients. However, a randomized, controlled trial evaluating cancer recurrence could not demonstrate such a connection via an immune modulation [15].

More recently, a Cochrane meta-analysis of 36 studies concluded that data support the hypothesis that perioperative blood transfusions have a detrimental effect on the recurrence of curable colorectal cancers. However, owing to the heterogeneity of studies and conclusions on the effect of surgical technique could not be drawn; a causal relationship between blood transfusion and recurrence of cancer cannot still be claimed [16].

**Transfusion in surgical patients with coexisting cardiovascular disease**

The Hb threshold value for blood transfusion in coronary patients is still controversial. During hemodilution, the heart is responsible for the compensation of dilutional anemia by an increase in CO and thus oxygen extraction. In the presence of coronary artery disease, the cardiac compensatory mechanisms of dilutional anemia are still preserved at Hb concentration of around 10 g/dL even when receiving chronic beta-blockade treatment. The compensatory mechanisms are independent of age or preoperative left ventricular ejection fraction [17] Hébert et al [18] have found that in intensive care unit (ICU), 30 day mortality in patients with cardiac morbidity was identical with either a restrictive transfusion strategy (target Hb 7-9 g/dL) or liberal transfusion strategy (target Hb 10-12 g/dL), with the possible exception of patients who were suffering from acute myocardial infarction or unstable angina, in whom a more liberal strategy may be beneficial. Whether patients with acute coronary syndromes may benefit from higher Hb concentrations (11-12 g/dL) is still a matter of debate [19, 20].

Koch et al [21] examined the effect of RBC transfusion and other blood components on morbidity after coronary artery bypass graft (CABG). Perioperative RBC transfusion was found as a single factor most reliably associated with increased risk of postoperative morbidity, such as mortality, renal failure, prolonged ventilatory support, infections, cardiac complications and neurologic events. However, in despite of this, Vincent et al [22], investigating the correlation between blood transfusion and mortality in intensive care units, found that blood transfusions were not associated with increased mortality rates in acutely ill patients.
Alternative strategies to allogeneic red blood cell transfusion and blood component therapy

In view of the increased potential for complications associated with blood transfusion, alternative strategies to blood transfusion are more frequently being recommended perioperatively. In order to elaborate restrictive transfusion strategies, it is necessary to determine the likelihood of transfusion requirements. In clinical practice, there are three main factors that determine transfusion requirements: 1) patient-related factors (i.e., preoperative blood volume); 2) type of surgery and clinical experience of the attending medical team, and 3) the transfusion policy of each institution. A detailed review of these strategies is beyond the scope of this manuscript.

The following list enumerates some alternative strategies that aim at decreasing perioperative allogeneic RBCs transfusion:

1. Preoperative autologous donation (PAD)
2. Preoperative use of erythropoietin
3. Acute normovolemic hemodilution
4. Red cell salvage
5. Use of artificial oxygen carries
6. Strategies related to the anesthetic approach:
   • Maintaining normothermia
   • Optimal fluid replacement for maintaining of normal blood volume and coagulation
   • Hyperoxic ventilation
   • Hypotensive anesthesia (deliberate hypotension)
7. Pharmacologic prevention of massive bleeding (aprotinin, epsilon-aminocaproic acid, tranexamic acid, desmopressin)
8. Other factors and strategies:
   • Acceptance of minimal hemoglobin level
   • Transfusion algorithms based on coagulation monitoring

All these techniques have been effectively applied in specific situations, thus avoiding unnecessary allogeneic RBCs transfusions [13].

Whenever necessary, various blood products should be administered, each with its specific indication, composition and potential for side-effects.

Transfusion guidelines

As emphasized above, the decision of blood transfusion should be based mainly on the patient’s individual ability to tolerate and compensate for anemia. Therefore, appropriate transfusion guidelines should take into consideration the physiological requirements justifying blood transfusion. While considering a certain blood transfusion strategy, it is crucial to promptly rule out and correct hypovolemia if present. Global signs of inadequate oxygenation and blood loss are hemodynamic instability, tachycardia and hypotension, as well as increased serum lactate and base deficit [23]. Other useful indicators are oxygen extraction ratio > 50%, mixed venous saturation < 50% and a decrease in oxygen consumption [3].

Preoperative evaluation should include reviewing medical records, conducting physical examination and identifying risk factors for organ ischemia (which may affect the transfusion trigger for RBCs) and coagulopathy. For elective surgeries, patient preparation should also consider discontinuation of anticoagulants in surgeries with a high propensity for bleeding, although recently, more liberal guidelines recommend the continuation or only a minimal reduction in dose of the anticoagulants, perioperatively.

The perioperative management of blood loss and transfusion should also consider close monitoring of the amount of blood loss, monitoring of hemoglobin or hematocrit, maintaining adequate perfusion and oxygenation to vital organs, and the preferences for normovolemic hemodilution and intraoperative RBC recovery [24].

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Red blood cell transfusion

In 2006 the American Society of Anesthesiologists launched a task force to establish new guidelines for blood component therapy, intended to develop evidence-based indications for transfusion of red blood cells, platelets, fresh frozen plasma and cryoprecipitate in the perioperative and peripartum setting [3]. The ASA transfusion guidelines strongly recommended the administration of red blood cells with hemoglobin level less than 6 g/dL. The determination of whether intermediate Hb concentrations (6-10 g/dL) justify or require RBC transfusion should be based on patient’s risk for complications of inadequate oxygen carrying capacity. Special consideration and lower transfusion thresholds may be required in patients aged > 80 yr., those with coronary artery disease, and patients with fever and hypermetabolic states. Furthermore, the task force emphasized that the use of a single Hb transfusion “trigger” (i.e., 6 or 10 g/dL) for all patients is not recommended. The task force also considered that when appropriate, preoperative autologous blood transfusion, intraoperative and postoperative blood recovery (by cell saver), acute normovolemic hemodilution, and the use of measures to decrease blood loss (deliberate hypotension), may be beneficial.
Platelets transfusion

Platelets count should be usually obtained before platelets transfusion and their function should be assessed in patients with drug-induced platelets dysfunction. In surgical and obstetric patients with normal platelets function, platelets transfusion is rarely indicated if their count > 100,000/µL, and usually indicated when the count < 50,000/µL. Platelets transfusion may be indicated with normal count if there is a suspicion of dysfunction (i.e., in the presence of microvascular bleeding); in cases of thrombocytopenia caused by increased platelets destruction (i.e., cardiopulmonary bypass). Prophylactic transfusion is ineffective and rarely recommended.

Fresh frozen plasma transfusion

Coagulation tests (PT or INR and PTT) should be obtained if possible before fresh frozen plasma (FFP) administration in the bleeding patient. The above ASA guidelines also recommend that FFP should not be used as volume expander, or in the presence of normal clotting function (i.e., preventive administration). Its administration is indicated only where excessive microvascular bleeding exists due to massive blood transfusion (≥ 70 ml/kg), in case of abnormal INR or prothrombin time, for urgent reversal of the effect of warfarin (coumadin), the correction of an unknown coagulopathy, or with heparin resistance due to antithrombin–III deficiency.

Transfusion of cryoprecipitate

The patient’s fibrinogen blood level should be measured before cryoprecipitate is administered. Replacement is rarely indicated if serum fibrinogen level > 150 mg/dL. It is indicated with excessive microvascular bleeding, when fibrinogen concentration < 80-100 mg/dL, during/following massive bleeding, or in patients with congenital fibrinogen deficiencies.

Recombinant activated factor VIIa (rFVIIa)

The use of rFVIIa was initially approved for patients with hemophilia who had developed inhibitors to factors VIII or IX. There is little experience in trauma patients, and most of the studies are case series or retrospective reports. The standard dose of 90 µg/kg was first used in hemophilias. Others used a median dose of 120 µg/kg (ranging 120-210 µg/kg). Aggarwal et al found that rFVIIa was effective in decreasing blood products usage and promoting hemostasis in patients with intractable bleeding associated with cardiac surgery and a variety of other causes. However, arterial and venous thromboses have been reported as serious complications of the treatment with rFVIIa. Further prospective, randomized, controlled trials are needed before founded recommendations regarding the role of rFVIIa in the management of traumatic bleeding can be emanated.

Conclusions and recommendation

Before a decision is made to transfuse blood or blood products to a patient for the treatment of anemia, all the clinically and physiological potential benefits, risks and cost issues ought to be weighed considering the individual patient in the context of the patient’s condition/pathology. Especially since there are no evidence-based recommendations in this regard, one should take into account whether alternative therapies can substitute or be incorporated in the treatment before opting for blood transfusion. In normovolemic patients with adequate cardiopulmonary function, acute anemia is usually well tolerated and therefore transfusion may be postponed or even annulled. There is still an ongoing controversy regarding this issue in patients with concomitant cardiovascular disease. More controlled data are necessary to determine whether perioperative blood transfusion is beneficial in patients with stable coronary heart disease, in cancer patients with acute bleeding and in those with immunologic pathologies.

References

Transfuzia sangvină perioperatorie: puncte de vedere pro și contra

Rezumat

În tratamentul anemiei, potențialele beneficii trebuie apreciate ținând cont de riscuri, costuri și accesul limitat la produsele de sânge. Alternativele la transfuzia de sânge, precum donarea de sânge preoperatorie și intervențiile farmacologice (de ex., eritropoietină, suplimentarea cu fier i.v. etc.) ar trebui avute în vedere înainte de a decide transfuzia. La pacienții normovolemici cu o funcție cardiovasculară adecvată, anemia acută este de obicei bine tolerată. De aceea, hemodiαuiția acută normovolemică, eventual combinată cu donarea autologă preoperatorie și/sau recuperarea intraoperatorie a hematiilor poate reduce cerința pentru transfuzia perioperatorie de sânge omolog.

Un nivel prag universal al hemoglobinei pentru indicarea transfuziei de sânge nu a fost încă stabilit. Pacienții cu boli coexistente (în special patologia cardiovasculară) potențial ar beneficia de un nivel mai ridicat al hemoglobinei. Totuși nu există date care să susțină necesitatea unui nivel prag mai ridicat al hemoglobinei pentru transfuzia perioperatorie.

Transfuzia produselor de sânge este asociată de riscuri, unele amenințătoare pentru viață; de aceea, indicația de transfuzie trebuie cântărită individual, pe baza aprecierii raportului risc-beneficiu. Cu toate acestea, în practica clinică, chirurgii și anestezistii au o politică liberă în prescrierea produsilor de sânge.

Scopul acestui scurt referat este de a atrage atenția cătoror asupra potențialului pericol asociat cu transfuzia de sânge și de a discuta măsurile alternative existente de contracarare a anemiei acute perioperatorii.