Transfusion and Management of Surgical Patients with Hematologic Disorders

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Surgeons frequently encounter patients with hematologic disorders in the perioperative period. A fundamental understanding of the cause and the management of these clinical derangements is required. Most of these derangements occur as a result of abnormal production, dysfunction, or rapid loss.

This section explores the recent literature and how it has transformed how blood is used in the surgical patient, how blood transfusions impact other patient outcomes, and the current treatment schemes of the massively transfused patient.

LIBERAL VERSUS CONSERVATIVE TRANSFUSION

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KEYWORDS

- Transfusion • Massive transfusion protocols • Transfusion-related lung injury • Transfusion-related outcomes

KEY POINTS

- In the hemodynamically stable patient, restricted use of packed red blood cells appears to be at least equal to liberal use of packed red blood cells.
- The use of fresh frozen plasma and platelets along with packed red blood cells in the massively transfused patient appears to be of benefit.
- Transfusion-related lung injury is one of the leading causes of mortality in the transfused patient.
- Meta-analysis suggests that transfused patients with colorectal cancer have worse outcomes when compared with nontransfused patients.

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Recently, there has been a paradigm shift in packed red blood cell (PRBC) utilization. The studies that compare liberal versus restrictive transfusion policy and how these they impact patient outcomes are examined.
Since the development of blood banks through the significant contributions of Dr Charles Drew around the beginning of World War II, the medical community has had many paradigm shifts on the appropriate clinical triggers for transfusion. In the acutely injured bleeding patient, the benefits outweigh the risks associated with blood transfusion. In all other surgical patients, the current paradigm would suggest that conservative clinical triggers provide the benefit and mitigate the risk. For many years, most clinicians used the 10/30 rule as a clinical trigger for transfusion of PRBCs. Because of concerns over transmission of blood-borne diseases and costs associated with a liberal transfusion rate, a re-examination of that clinical trigger began in the 1980s and continues to date. The 1988 National Institutes of Health Consensus Conference concluded that no one criterion should be used as an indication for transfusion and that multiple patient factors should be considered.1 Since that time, many associations have published many guidelines in an attempt to determine the elusive trigger.2–5 The indications and thresholds for PRBCs transfusion in adults are discussed in this section.

The support for a liberal transfusion protocol was developed primarily through observational studies that identified an association between anemia and poor outcomes.

- In a 1958 study of patients who declined blood transfusions for religious reasons, the mortality increased as the preoperative hemoglobin (Hgb) decreased.6
- That study had a mortality of 61.5% in the patients with an Hgb of less than 6.
- Patients with an Hgb of greater than 10 had a 7.1% mortality.7
- These observational studies help formulate the 10/30 rule.

Also, studies suggested that there were groups of anemic patients that were at high risk for poor outcomes. Geriatric patients and patients with coronary artery disease are the groups that were determined to be most at risk when anemic in the perioperative period. When a patient is anemic, there are physiologic changes that occur to compensate for the anemia and hemodilution. Many articles describe the association of hemodilution and normalization of tissue oxygen delivery through increasing cardiac output.7,8 However, in patients who cannot increase stroke volume because of coronary artery disease and/or decreased physiologic reserve, compensating during periods of anemia becomes the challenge.

- Multiple studies did not demonstrate worse outcomes with hemodilution; the animal studies illustrated that the hemodilution was mitigated by increased stroke volume and cardiac output in the animals with normal physiology. Patients who cannot increase their stroke volume or cardiac output have worse outcomes when they are anemic.9

The geriatric patient is a patient that surgeons care for frequently in the United States. Because anemia is quite prevalent in this population, many of these patients present anemic with a need for surgical intervention.

- Based on the World Health Organization definition of anemia, which is an Hgb less than 13, 10% of patients 65 to 84 and 25% of patients 85 and older are anemic.
- Perioperative anemia constitutes a bad prognosis and increased mortality in elderly patients.10
- Symptomatic anemia and severe anemia should always be treated in the elderly.
- One observational study revealed a benefit for liberal transfusion rate in the elderly population.11
A recent clinical trial, Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture, found the following characteristics:
- Average age of 78
- Cardiac disease or coronary artery disease in 63% of the patients
- No differences in functional outcome or mortality when restrictive versus liberal transfusion triggers were used
  - Higher myocardial infarction rate in the restrictive group, but not statistically significant.

The current literature does not support a liberal transfusion policy for the noncardiac and nongeriatric patient population. The recent prospective clinical trials and meta-analysis point toward a restrictive transfusion policy that has equal or better clinical outcomes when compared with a liberal policy.

- The transfusion requirements in critical care trial did not find a benefit in keeping Hgb between 10 and 12 when compared with keeping Hgb between 7 and 9.
  - Liberal cohort trended toward worse mortality.
  - Ages 55 and younger had statistically worse outcomes when liberally transfused.
    - Mortality
    - Myocardial infarction
    - Congestive heart failure
- None of the current clinical trials reported statistically significantly higher mortality, and cardiac morbidity, infections, and length of hospital stay were associated with a lower use of red blood cell (RBC) transfusion.
- In-hospital mortality and infections are associated with a liberal use of RBCs.

Clinical Recommendations Made by the American Association of Blood Banks Clinical Transfusion Committee

In hospitalized, hemodynamically stable patients, at what Hgb concentration should a decision to transfuse be considered?

- The American Association of Blood Banks (AABB) recommends adhering to a restrictive transfusion strategy.
  - In adults and pediatric intensive care unit (ICU) patients, transfusion should be considered at Hgb concentrations of 7 g/dL or less.
  - In postoperative surgical patients, transfusion should be considered at an Hgb concentration of 8 g/dL or less or for symptoms (chest pain, orthostatic hypotension or tachycardia unresponsive to fluid resuscitation, or congestive heart failure).
  - Quality of evidence: high
  - Strength of recommendation: strong

In hospitalized, hemodynamically stable patients with pre-existing cardiovascular disease, at what Hgb concentration should a decision to transfuse RBCs be considered?

- The AABB suggests adhering to a restrictive transfusion strategy.
  - Transfusions should be considered at an Hgb concentration of 8 g/dL or less or for symptoms (chest pain, orthostatic hypotension or tachycardia unresponsive to fluid resuscitation, or congestive heart failure).
  - Quality of evidence: moderate
  - Strength of recommendation: weak
In hospitalized, hemodynamically stable patients with acute coronary syndrome, at what Hgb concentration should an RBC transfusion be considered?

- The AABB cannot recommend for or against a liberal or restrictive RBC transfusion threshold.
- Quality of evidence: very low
- Strength of recommendation: uncertain.

In hospitalized hemodynamically stable patients, should transfusion be guided by symptoms rather than Hgb concentrations?

- The AABB suggests that transfusion decisions be influenced by symptoms as well as Hgb concentrations.
- Quality of evidence: low
- Strength of recommendation: weak.

MASSIVE TRANSFUSION

An additional hematologic disorder encountered in the perioperative period is coagulopathy, typically seen in the critically ill patient; however, with timely recognition and proper treatment, good outcomes are attainable. Coagulopathies usually are a result of underlying clinical conditions, such as hepatic insufficiency, medication use such as Coumadin, injuries associated with hemorrhagic shock, or massive tissue destruction. This section examines how trauma-related coagulopathy has guided the scientific efforts and development of current treatment protocols of the massively transfused patient.

The definition of massive transfusion is to replace a person’s blood volume within a 24-hour period; this is roughly equivalent to transfusing 10 units of PRBCs in an adult. The coagulopathy associated with massive transfusions is a result of dilutional and consumptive processes. Traumatic injuries that usually require massive transfusions cause the consumptive thrombocytopenias and coagulopathies. Furthermore, the dilutional effect of transfusing multiple units of PRBCs combined with infusing large volumes of crystalloid has led to the development of irreversible coagulopathies. Management of these critically ill patients requires close clinical observation and frequent laboratory evaluations. Surgeons should avoid hypothermia, hypovolemia, and acid/base imbalances and correct all coagulation and electrolyte abnormalities. Because of the frequency that irreversible coagulopathy is associated with massive transfusions, it is recommended that fresh frozen plasma (FFP) and platelets be transfused along with the PRBCs. However, there has been some debate over the optimal transfusion ratio of blood products.

Coagulopathy complicates the care of the critically injured patient; the liberal transfusion of FFP and PRBCs can be equally detrimental to this patient population. Transfusion of PRBCs to restore oxygen delivery and FFP to correct the associated coagulopathy has produced higher rates of multiorgan failure (MOF).

- A 2010 study identified that the absolute amount of FFP and the increased ratios of FFP and PRBCs increased the rate of MOF in the critically injured patient.16
- Another study looked at the non-massively transfused patient and found that the FFP transfusion was associated with increased complications17:
  - Acute respiratory distress syndrome
  - MOF
  - Pneumonia
Long-term functional outcomes appear to be compromised when patients receive massive transfusion protocol (MTP).\(^\text{18}\)

Another study did identify an overuse of MTPs in the nontrauma patient but did not identify a higher rate of adverse outcomes.\(^\text{19}\)

Acute traumatic coagulopathy (ATC) is the driving force behind the development of MTP, but the mechanisms and physiologic process that influence ATC are not completely understood. In the critically injured patient, presenting ATC is considered treatable, but there are risks associated with overuse of MTP. Currently, thromboelastography (TEG) is reported as a possible laboratory test that can help identify and guide the resuscitation.

Initially, it was considered that iatrogenic causes (dilution, hypothermia, and acidosis) contributed to the development of ATC.

There are endogenous processes that occur before and independent of the iatrogenic processes.

The prospective, observational, multicenter major trauma transfusion (PROMMTT) study did identify ATC in the prehospital setting in 42.7% of the patients.\(^\text{20}\) The major contributors to the endogenous factors were as follows:

- Coagulation factor depletion as a result of tissue injury
- Coagulation factor dysfunction associated with shock

Early platelet dysfunction has been found to contribute to ATC. A recent study identified that trauma patients presented with normal platelet counts but profound platelet dysfunction.\(^\text{21}\)

This dysfunction was associated with the following:

- Injury severity
- Blood transfusion
- Shock or base deficit of greater than or equal to 8.

Although prothrombin time/partial thromboplastin time (PT/PTT), international normalized ratio (INR), and platelet levels are considered standard laboratory values to identify ATC, these tests were not developed to evaluate the acutely or critically injured patient. Also, they are not typically helpful during the hemostatic resuscitation.

PT/INR and PTT fail to quantify clotting beyond the initiation phase. TEG and rapid TEG allow for the evaluation of how all of components are functioning as a unit.\(^\text{22}\)

Multiple studies confirmed that early use of TEG technology, FFP, and platelet transfusion in the massively transfused patient decreases mortality and treats ATC.\(^\text{22–24}\)

Currently, there are multiple observational studies that suggest that MTP decreases mortality in the critically injured patient. A better understanding of the mechanisms and timing of ATC, along with studies that confirm that the early use of platelets and FFP decrease mortality, suggests that efforts are moving in the right direction. However, there are studies identifying the in-hospital and long-term risks associated with these protocols. The hope was that the recent clinical trials would alleviate the controversy. The data from the PROMMTT suggest that transfusion ratio greater than 1:2 for plasma:RBC and platelet:RBC within 6 hours of hospitalization improves outcomes.\(^\text{25,26}\) The pragmatic randomized optimal platelets and plasma ratios trial is ongoing, and it is hoped it will provide some additional useful data on the topic.

**Clinical Recommendations and Key Points**

- PRBC transfusion is indicated for patients in hemorrhagic shock.\(^\text{20}\)
• International and national trends are to move toward a formula-driven MTP incorporating point-of-care testing (TEG) to guide the ongoing transfusions.
• MTP with RBC:plasma:platelets ratios of 1:1:1 appears to improve survival in the critically injured patient, but additional data are needed.

TRANSFUSION-RELATED OUTCOMES

Many side effects to transfusion have been reported in the literature. Despite appearing in the literature, often the incidence and many of the mechanisms that promote these poor outcomes are not completely known. Transfusions are associated with the transmission of blood-borne pathogens, higher mortality, longer hospital stays, transfusion-related acute lung injury (TRALI), and poor outcomes in patients with cancer. Although some of these poor outcome measures have been discussed earlier, the mechanisms and risk factors associated with some of the transfusion-related poor outcomes that are pertinent to surgical patients are explored.

Transfusion-related Acute Lung Injury

TRALI is a clinical syndrome that presents as acute hypoxemia and noncardiogenic pulmonary edema during or after blood transfusion. TRALI is a leading cause of mortality in the transfused patient. Historically, this was underreported and underdiagnosed; however, work groups have brought needed attention to TRALI over the past decade.

• All transfused blood components (PLT, RBC, and FFP) have a risk of inducing TRALI.
• The true incidence of TRALI is unknown.
• A 2011 study of consecutive cardiac patients identified a possible incidence of 2.4% in transfused patients.  
  ○ An amount of 0.61% of blood products was transfused.
  ○ Only 1 patient was reported to the blood bank.
• The pathophysiology of TRALI is increased pulmonary microvascular permeability along with increased protein in the edema fluid.
• Two unique but not mutually exclusive mechanisms have been proposed as the cause of TRALI.
  ○ Transfused leukocyte antibodies reported a higher incidence with blood transfused from multiparous women and a higher percentage of lymphocyte and granulocyte antibodies in the transfused blood.
  ○ The 2-hit theory is that a stressor (surgery, trauma, or sepsis) sequesters neutrophils in the lung. The second hit occurs with the transfusion of biologically active substances such as lipids or cytokines.
• In confirmed cases of TRALI that were studied in a prospective manner, the TRALI patients had longer hospital and ICU stays, more days on the ventilator, and higher mortality.

Cancer Outcomes and Transfusions

Surgery is the cornerstone of any multidisciplinary treatment plan for most solid organ malignancies. To improve outcomes, investigators constantly examine variables that will improve morbidity and mortality associated with treatment plans. Over the past 2 decades, the impact of surgical blood loss on outcomes in patients with cancer has been examined. Because many of these patients present with anemia, the surgical blood loss compounds this problem and usually results in a high transfusion rate in the perioperative period. Recently, the impact of blood transfusions on cancer-related outcomes has been debated in the literature and is examined in this section.
Perhaps the most intuitive clinical outcome of presenting anemia in the surgical oncology patient is the subsequent perioperative blood transfusion. Despite evidence that anemia is associated with poor patient outcomes, correction of this anemia has not improved these outcomes.

- A small, randomized study could show no benefit of a liberal transfusion policy (Hgb >10) compared with a restrictive transfusion policy (Hgb 8.5–10) in patients with resected lung cancer.30

It is estimated that the prevalence of anemia in the surgical oncology patient population is 25% to 75%, depending on the disease site.31 Gastric cancer has one of the highest incidences of associated perioperative anemia. Most patients with gastric cancer require a total or subtotal gastrectomy and some form of lymph node dissection, and many have undergone some form of neoadjuvant therapy. The combination of presenting anemia and radical surgery usually results in the use of perioperative blood transfusion to correct the anemia.

- A retrospective study of 856 patients who had an R0 resection found that transfusion was an independent predictor of poor survival across all stages of disease.32
- The need for transfusion was significantly related to the T stage, preoperative albumin, Hgb, and operative time.33
- Also, this study found that blood transfusions were related to decreased patient survival, but the authors thought that the survival relationship was confounding and not prognostic.33

Another gastrointestinal tract malignancy associated with perioperative anemia and a high incidence of perioperative blood transfusion is colorectal cancer. There are some similarities between gastric and colorectal cancer, but colorectal cancer has a higher incidence and an opportunity to control the confounding variables. This section explores how blood transfusion impacts colorectal cancer–related treatment outcomes.

- Retrospective studies identified a negative relationship between perioperative blood transfusion and survival of the patient with colorectal cancer.34
- The authors thought that this relationship was confounded by many variables as stated above. Small prospective trials attempted to control for some of these variables.
- One proposed variable investigated the banking process of the allogeneic blood; this study randomized patients to receive leukocyte-reduced blood (LR), buffy coat depleted blood (BCD), or no blood transfusion (NT).35
  - Initial results found that blood transfusion regardless of how it was processed had a detrimental effect on overall survival.
  - However, the 15-year follow-up results found that 43% of the NT, 27% of the LR, and 28% of the BCD patients were alive at 15 years.
- Some authors thought the cause of the worse outcome could be explained by the difference between allogeneic and autologous blood transfusion. A randomized trial of 475 patients with a 30-month follow-up found that the transfused patients, regardless of whether it was allogeneic or autologous, did worse.
  - Worse local recurrence rate
  - Worse disease-free interval.
- The 20-year follow-up of that study found that there was no survival benefit to blood transfusion regardless of whether it was autologous or allogeneic.36
With the conflicting results of the small trials, meta-analyses were performed to try to answer the question. Large meta-analyses found that transfused patients had worse clinical outcomes when compared with nontransfused patients.\(^3\) All-cause mortality, cancer-related mortality, recurrence or metastatic-related death, postoperative infections, and length of hospital stay. This study had no patient-related or stage-related data. Cochrane analysis and meta-analysis found that perioperative blood transfusion increased the recurrence rate in patients with curable colorectal cancer. The heterogeneity detected in the study prevents the authors from assessing a causal relationship.\(^3\)

Most of the data support the notion that perioperative blood transfusions negatively impact outcomes related to the patient with cancer. Because many of these patients present with anemia, consideration should be given to the development of an anemia management plan. This plan should focus on the correction of preoperative anemia with bank blood alternatives, minimization of perioperative blood loss, and the use of restrictive transfusion triggers.

PERIOPERATIVE MANAGEMENT OF SPECIFIC HEMATOLOGICAL DISORDERS

**Von Willebrand Disease**

Von Willebrand disease is the most common inherited abnormality affecting platelet function. It is caused by a deficiency or dysfunction of von Willebrand factors (vWF) that are essential to a platelet’s adhesion. Common symptoms reported with this disorder are related to the skin and mucous membrane and include mucosal bleeding, gastrointestinal bleeding, menorrhagia, epistaxis, and easy bruising; however, because vWF is also a carrier protein for factor VIII (FVIII), these patients may also have prolonged active partial thromboplastin time (aPTT).

Preoperative evaluation should therefore include measurement of FVIII activity, vWF activity, and ristocetin cofactor activity laboratory tests to appropriately assign severity of the disease. Type 1 vWD or mild disease represents a partial quantitative deficiency in vWF; type 2 disease is dysfunctional vWF/qualitative deficiency, and type 3 or severe vWD is a complete deficiency of vWF.

**Recommendations**

Although the effectiveness of desmopressin (DDAVP) depends on the disease type, all surgical patients with vWD require preoperative desmopressin at 30 $\mu$g/kg intravenously over a period of 30 minutes or vWF/FVIII concentrate for surgical prophylaxis and a consultation by a hematologist. FVIII and vWF levels usually increase 30 to 60 minutes after administration of desmopressin and stay at that level for 8 to 10 hours. Desmopressin can be repeated in 12 to 24 hours for up to 36 hours if the patient has postoperative bleeding. The vWF/FVIII concentrate is indicated for patients who do not respond to desmopressin with concentrate dosing at 25 to 50 IU/kg depending on the FVIII activity and monitored every 12 hours for the first 24 hours and then every 24 hours, avoiding supratherapeutic levels.

**Hemophilia A/B**

Congenital FVIII deficiency (hemophilia A) and factor IX deficiency (hemophilia B) are coagulopathies that require perioperative management in surgical patients because they are associated with an increased risk of excessive bleeding with surgery. These patients usually have a prolonged aPTT and a normal PT.
Hemophilia A is an X-linked recessive disorder caused by a mutation of the FVIII gene. Its severity is proportional to FVIII level and activity. Severe hemophilia A has FVIII levels less than 1% of normal and so is usually diagnosed in childhood and is usually known by the patient before any surgery hence the importance of an excellent history. Patients with factor levels between 6% and 30% of normal are considered mildly affected and may go undiagnosed, because they do not spontaneously bleed into vital organs.

Hemophilia B is also an X-linked recessive disorder caused by a mutation in factor IX gene leading to factor IX deficiency.

**Recommendations**

Plasma-derived or recombinant FVIII or factor IX concentrate should be given as surgical prophylaxis before any surgical intervention and continued for 10 to 14 days following the procedure. The initial dose can be 50 to 60 U/kg (for hemophilia A) or 100 U/kg (for hemophilia B) depending on the factor activity level and can be repeated with doses of 25 to 30 U/kg every 8 to 12 hours for hemophilia A or 30 to 50 U/kg every 12 to 24 hours for hemophilia B if the respective factor levels drop to less than 80%. A consultation with a hematologist is recommended; the dosage required is to reach 80% to 100% of normal factor activity.

**Idiopathic Thrombocytopenic Purpura**

Idiopathic thrombocytopenic purpura (ITP) disorder is also known as primary immune thrombocytopenic purpura, and it involves antibodies against platelet antigen formed and leading to destruction of the platelets, hence thrombocytopenia. The immune-complex-coated platelets are destroyed and eliminated by the spleen. The patient presents with thrombocytopenia not related to drugs or other causes, and it is a diagnosis of exclusion. ITP can present as an acute form or a chronic form. Clinical features of ITP are different in adults and children, occurring acutely in children after a viral infection but self-limiting. In adults, it can be an acute onset but usually with no preceding infection and then proceeds to a chronic form with a high production rate of platelet in the bone marrow in an effort to maintain a low to near-normal platelet count. Presentation is highly variable, ranging from asymptomatic to mild symptoms of easy bruising and gastrointestinal bleeding, to severe symptoms such as intracranial bleeding.

**Recommendations**

If the surgical patient with ITP presents with bleeding, ITP should be treated as a medical emergency with high-dose corticosteroids for the first 3 days. The patient should also receive intravenous immunoglobulin and platelet transfusion every 8 to 12 hours. There are some adults who do not respond to corticosteroids and develop chronic ITP. Splenectomy is often recommended, but the patient will require pneumococcal, meningococcal, and haemophilus influenza vaccines before surgery.

**REFERENCES**


