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Blood Transfusion Therapy in High Risk Surgical Patients

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1. Introduction

Anemia is common in surgical patients. The number of patients transfused with red blood cell (RBC) in the United States increased from 12.2 million, to more than 14 million most recently, specially in the perioperative period (Park et al. 2004). Anemia is associated with considerable morbidity and poor outcome. Equally, blood transfusion has been related to worse outcome, including in surgical patients (Sakr et al. 2010).

Transfusion is the cornerstone of treatment for serious anemia in this population, to restore oxygen carrying capacity, consequently, reducing tissue hypoxia. Vincent and colleagues reported a 37% transfusion rate in intensive care unit (ICU) patients, and directly 73% of patients who remained in the ICU more than one week received transfusion (Vincent et al. 2002). Similarly, Taylor and colleagues found 85% transfusion rate among patients who stayed in the ICU more than seven days (Taylor et al. 2002).

Blood transfusion was independently associated with organ failure, longer ICU length of stay and increased risk of death. Possible, because deleterious effects of transfusions, especially, immunosuppression that is associated with nosocomial infection and directly related to the number of packed red cells unit used (Taylor et al. 2002).

Another complication is the transfusion-related acute lung injury (TRALI). TRALI is determined as a non-cardiogenic pulmonary edema, temporary related to the transfusion (Looney et al. 2004).

Besides, there were no radical changes in transfusion practice over time. Recent study has demonstrated that mean pre-transfusion hemoglobin was about 8.0g/l. In 30% of patients hemoglobin concentrations are targeted above 9g/dl (Silva Jr et al. 2008).

Hébert and colleagues, in a randomized controlled study, investigated the impact of two different therapeutic strategies for anemia in ill critical patients (Hebert et al. 1999). A restrictive transfusion strategy (hemoglobin concentrations targeted above 7g/dl) was as effective as and maybe more efficient than a liberal strategy (hemoglobin concentrations targeted above 10g/dl). A subgroup of patients that presented unstable angina was

excluded. According to this evidence, it is recommended a blood transfusion trigger of 7.0g/dl for ICU patients.

The cause of anemia in these patients is likely to be multifactorial.

Intraoperative:
Loss of blood:
Surgery, trauma
Blood sampling
Other bleeding
Postoperative:
Gastrointestinal bleeding
Less production
Lower red cells production:
Lower erythropoietin synthesis
Erythropoietin resistence
Iron shortage
Erythrocytes half life decrease
Hemolysis increase

Table 1. Factors associated with anemia in peri-operative period

2. Blood transfusion epidemiology

Because of the high anemia incidence perioperatively, many patients will receive blood transfusion at some point. Many studies have appraised the blood transfusion epidemiology.

In a Canadian study, enrolling 5298 people, 25% from patients received blood transfusion (Hebert et al. 1999). In the United Kingdom, this number escalated to 53% of 1247 patients during length of ICU stay. The ABC study, in 146 ICUs from Western Europe, covered 3534 patients and showed 37% transfusion rate in ICU. Longer length of hospital stay was associated with blood transfusion (25% with 2 days, 56% with more than 2 days and 73% with more than seven days).

In the CRIT study, 44% of the patients received one or more transfusions in ICU (Corwin et al. 2004). The recent SOAP (*Sepsis Occurrence in Acutely ill Patients*) study showed a 33% transfusion incidence (Vincent et al. 2008).

Finally, a randomized study made with patients in postoperative period for cardiac surgery demonstrated that blood transfusion with hemoglobin trigger of 7 g/dl did not result in a worst clinical evolution. Otherwise, there was better outcome (Hajjar et al. 2010).

Authors	Year when the study was made	Number of patients	Transfusion percentage	Comments
Herbert et al	1999	5298	25%	Significant institutional variation was identified in the transfusion practice
Vincent et al	1999	3534	37%	For patients with similar levels of organ dysfunction, the ones who received blood transfusion displayed high mortality rates
Rao et al	1999	1247	53%	Average pre-transfusion hemoglobin was greater than 9g/dl in 75% of the transfusions
Corvin et al	2000/2001	4892	44%	The number of transfusions was associated with a greater length hospitalization and ICU stay, and greater mortality
Walsh et al	2001	1023	39,5%	Almost half of the transfusions were not associated with signifcant bleeding
French et al	2001	1808	19,8%	The most common transfusion indication was acute bleeding. Only 3% of the transfusions were considered inappropriate
Hajjar et al	2010	512	63%	As greater number of transfusions as greater mortality within 30 days. The restrictive strategy resulted in less complications

Table 2. Recent important studies assessing transfusion periodicity

3. Oxygen transportation

Hemoglobin (Hb) is essential to oxygen transportation. Human Hb is composed of 2 α and 2 β chains of polypeptides. One heme group transport one molecule of oxygen (1 g of Hb ties 1.39 mL of O2) and changes in hemoglobin affinity for oxygen correlates with change in red cell 2,3- Diphosphoglycerate (2,3-DPG) content, carbon dioxide, pH and body temperature.

The 2,3-DPG molecule binds to one of the b-chains of Hb favouring deoxygenation, reducing hemoglobin oxygen affinity. Thereby, low 2,3-DPG concentrations increases the Hb affinity to O2, dislocating the oxyhemoglobin dissociation curve to the left, described as P50 (PO2 at which the hemoglobin becomes 50% saturated with oxygen). P50 in adults is 26.3 mmHg (Moore et al. 2005).

The blood concentration of hydrogen ion or carbon dioxide reduces hemoglobin oxygen affinity, the Bohr effect. Otherwise, the Haldane effect states that deoxygenated Hb has a greater affinity for CO2 than does oxyHb. Only 10% of the carbon dioxide is removed from the tissues as carboxyhemoglobin, 80% is removed as bicarbonate and 10% remaining as physical solution.

In addition, low body temperature and high blood pH increases the Hb affinity to O2 and reduces P50.

4. Blood transfusion risks and benefits

Blood transfusion is safer today, however adverse are events still clinically relevant. The expected benefit is to improve the oxygen demand, preventing cellular injury. However, it is difficult to demonstrate these benefits in current clinical studies.

Risks related to blood transfusion are divided in infectious and noninfectious. Infectious risks include HIV transmission, estimated in 1:676,000 transfusions in the USA and transmission of A, B and C hepatitis virus, estimated in 1:1,000,000, 1:63,000 and 1:103,000, respectively (Goodnough et al. 2003).

Other viral infections related to transfusions are the human T-lymphotropic virus (HTLV) types I and II, the parvovirus B19 and the Creutzfeldt-Jacob disease, caused by a prion, causing encephalopathy with fast evolution to dementia.

As viral infections, bacterial infections are also frequent complications of transfusion. The contamination incidence is 1 per 1,000,000 transfusion units in USA. The most important bacterial infections are caused by gram-negative bacteria, such as *Yersinia enterocolitica, Serratia* and *Pseudomonas*, which have the ability to grow even between 1 and 6 ^{o}C. The contamination rate is associated with the blood packed storage time (Shorra et al. 2005).

Immunosupression is a noninfectious complication, that increase the risk of infection. Other noninfectious risks are related to acute lung injury and human error, when there is an incorrect identification of the patients or the red blood cell package. In this case, it can cause hemolytic reactions.

The transfusion related acute lung injury (TRALI) is one of the most serious complications by noninfectious causes and is defined as acute respiratory disease that happens within the first 4 hours after the transfusion. TRALI is distinguished by dyspnea and hypoxia due to noncardiogenic pulmonary edema. The incidence is about 1 to 5000 transfusions. The treatment is just support.

	Incidence frequency per a million units (for current unit)
Infectious	
Virus	
Hepatitis B	4 (1/220,000)
Hepatitis C	1 (1/800,000–1/1.6 X10^6)
HIV	1 (1/1.4–2.4 X10^6)
Bacteria	
Red blood cells	2 (1/500,000)
Platelets	500 (1/2,000)
Acute hemolytic transfusion reaction	1 to 4 (1/250,000–1,000,000)
Delayed hemolytic transfusion reaction	1000 (1/1,000)
TRALI	125 (1/8,000)

Adapted from Goodnough LT, et al. *New Engl J Med* 1999; 340:438–447.

Table 3. Risk estimates for blood transfusions.

Silva Jr. and colleagues reported a 57.5% incidence of post-operative complications in ICU patients. Mostly frequent, up to 28 days after the blood transfusion, and included infections (36.3%), changes in the markers of tissue hypoperfusion (30.0%), shock (22.5%), Acute Renal Failure (ARF) (12.5%), cognitive changes (11.33%), fistulas of the digestive tract (6.3%), and ARDS (5.0%) (Silva Jr et al. 2008).

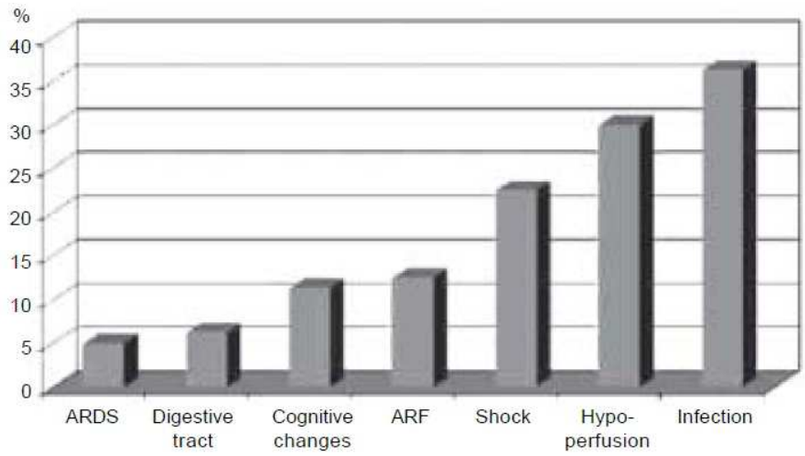

Fig. 1. Postoperative complications. Columns indicate the percentage of postoperative complications.

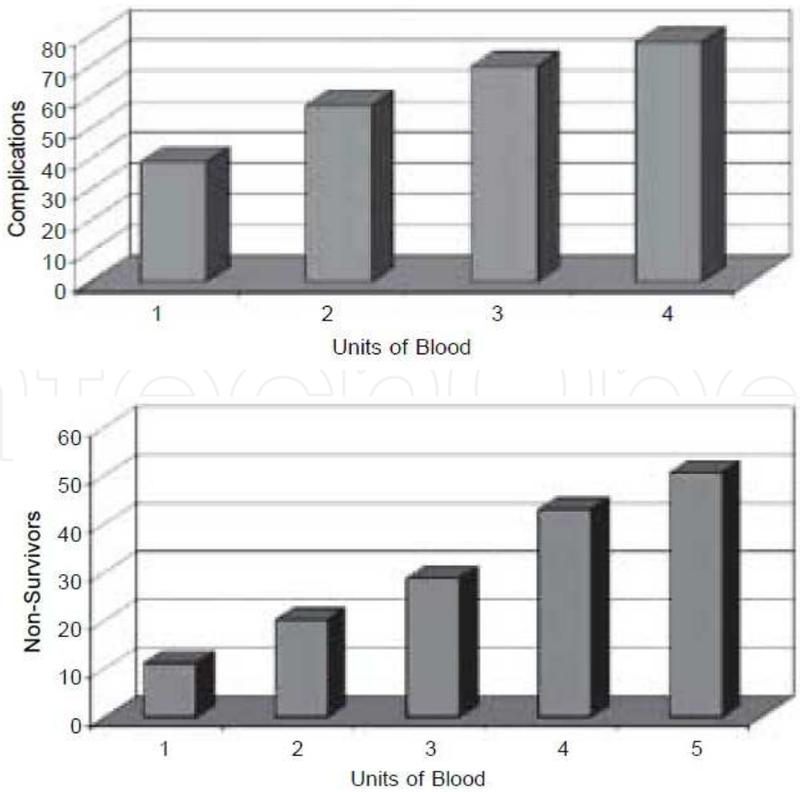

Fig. 2. Relationship between the Blood Number of Units and Morbi-mortality

In addition, the number of units of blood transfused was directly related to the incidence of these complications and mortality, i.e., the greater the number of units transfused intraoperatively, it was higher the chances of complications and death in the postoperative period. (Silva Jr et al. 2008)

5. Blood transfusion necessity assessment

The optimal transfusion trigger in ICU patients has been a matter of controversy. The ongoing debate about risks and benefits regarding blood transfusions is based on a individual assessment, considering diagnosis and comorbidities to help therapeutic aproach.

Serum concentrations of hemoglobin would be an easy reference and were used for years as a guide to start transfusions, but the optimal hemoglobin concentration varies considerably in each patient, according to several characteristics as age, preexisting chronic diseases (coronariopathy), current diagnosis and the cause of anemia.

Using the simple hemoglobin level, below which all patients should be transfused, and specific values for certain groups, are also rigid. The concept of critical hemoglobin level, defined as the minimal hemoglobin concentration while there is no pathological O2 supply dependency, seems to be a reasonable indication for blood transfusion.

There are some parameters to evaluate tissue hypoxia in clinical practice, like blood lactate, but this parameter indicates that the hypoperfusion is already in place and may be too late to indicate the point to start transfusion. However, a recent study in surgical patients demonstrated that transfused patients with high venous oxygen saturation had worse outcomes in the postoperative period (Silva JM et al. 2009).

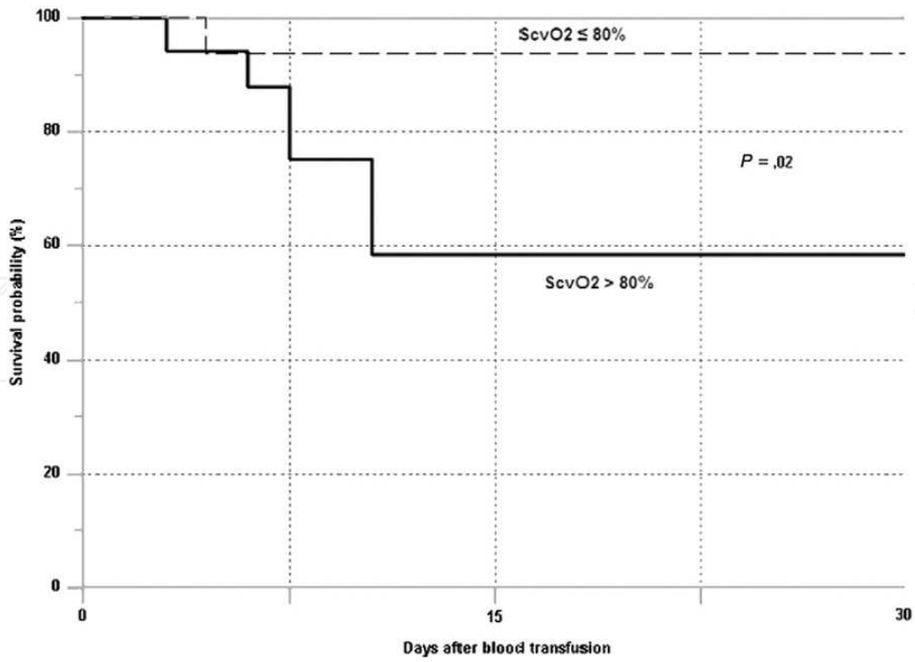

Fig. 3. Kaplan-Meier curve of transfused patients with ScvO2 80% or less and ScvO2 greater than 80%: (Silva JM et al. 2009).

Hébert and colleagues (Hebert et al. 2001) demonstrated in their study that, in critically ill patients, hemoglobin levels between 7 g/dl and 9 g/dl are safe (except in patients with myocardial infarction and unstable angina). Hajjar and colleagues (Hajjar et al. 2010) have also demonstrated that in postoperative cardiac patient hemoglobin level of 7 g/dl is safe and blood transfusion was associated with higher rates of complication.

Today the recommendations for septic hemodinamically stable or unstable patients are to maintain hemoglobin levels around 7g/dl before indicate transfusion. Besides, a study in health volunteers with isovolumetric hemodilution and hemoglobin concentration ≤ 5.0 g/dl, did not result in clear anaerobic metabolism (Weiskopf et a. 1998). Moreover, studies made with Jehovah's Witnesses patients showed that survival is possible even with lower hemoglobin levels. In a case report, a patient presenting hemoglobin level of 1.8 g/dL, had a acceptable evolution (Howell et al. 1998).

6. Strategies to avoid blood transfusion risks

There are several techniques to prevent blood transfusion, but they are summarized in blood loss optimization, blood cells production increasing and auto transfusion.

Several evidences show that the most effective way to increase blood production is the use of erythropoietin in preoperative period, but the time to reach recommended hemoglobin values is very long, making the process very slow and not useful.

Among the self-transfusion modes, there is the self preoperative donation (removing the blood before the surgery and, if needed, using it in the intraoperative or postoperative). This method is recommended only for patients above 20 kg . Besides that, this technique may be accompanied by hemodilution, allowed for patients with hematocrit above 35%. The blood is replaced, using crystalloid fluids to lower hematocrit to 25%, recommended for patients above 1 year old, because of the presence of fetal hemoglobin in neonates. Thus, this technique can be used shortly before surgery.

During the intraoperative, the self-transfusion can be performed using machines that reutilize the lost blood on surgery. In cardiac surgeries, the blood from the extracorporeal circulation circuit is returned. The same technique is difficult to be performed in children, because the lost blood is too small to be replaced.

In an attempt to prevent intraoperative blood losses, there are some measures such as desmopressin 0.3 ug/kg, which stimulates the release of von Willebrand factor, needed for platelets adhesiveness for damaged tissues, which does not apply to pediatric patients, and antifibrinolytics, preventing fibrinolysis and stabilizing clot formation. This last, in spite of reducing bleeding, it showed some harm potential, because it can cause thrombi, leading to myocardial ischemia and renal failure. Finally, the recombinant activated factor seven (rFVIIa) has shown positive evidence in patients with trauma and heavy bleeding.

Another way to avoid the transfusion risks is the minimal exposure to transfusion, in other words, transfusion from a single donnor and permissive hypotension, in an attempt to prevent blood losses. But we must consider the risks and benefits, being contraindicated in children under 2 years and patients with systemic diseases, showing vital organs damages.

The transfusion reactions risks can also be minimized by the using of the leukoreduction of blood, which means to remove leukocytes in transfused blood, resulting in less immunological effects because of the transfusion, such as alloimmunization to leukocyte antigens, febrile reactions and TRALI.

7. Massive transfusion

Massive transfusion defined as a whole blood volume changed within 24 hours, a replacement greater than 10 units of RBC packages within 24 hours, greater than 4 units of RBC packages within 1 hour or a 50% replacement of total blood volume within 3 hours.

So, the strategy used in intense and uncontrollable bleeding is to prevent the overuse of isotonic crystalloid solutions and to associate massive transfusions to early administration of products that help hemostasis (plasma, platelets and cryoprecipitate) in proportion to the blood transfusion, in other words, 1 erythrocytes concentrate: 1 plasma: 1 platelet, measure that has brought great benefits in patients requiring large transfusions.

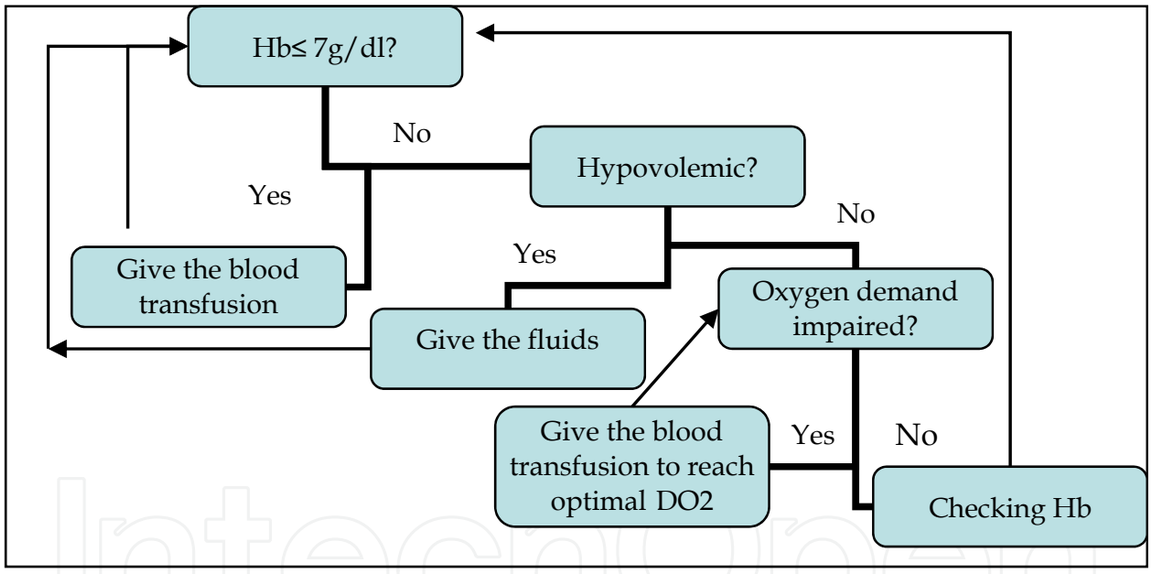

Fig. 4. Transfusion therapy summary in surgical patients.

8. Conclusion

Anemia is common in surgical patients and results in numerous blood transfusions. There are few evidences showing that blood transfusions are benefic to surgical patients. For those patients without active bleeding or acute cardiovascular disease, 7g/dl hemoglobin is well within tolerable limits. Besides hypoperfusion associated with low hemoglobin level appears to be an important indicator to be taken into consideration to decide for blood transfusion. Strategies to avoid blood losses and increase blood production may as well be an important tool for those patients.

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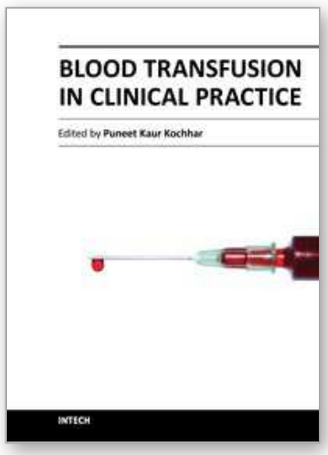

Blood Transfusion in Clinical Practice

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Blood Transfusion in Clinical Practice focuses on the application of blood transfusion in different clinical settings. The text has been divided into five sections. The first section includes a chapter describing the basic principles of ABO blood group system in blood transfusion. The second section discusses the use of transfusion in various clinical settings including orthopedics, obstetrics, cardiac surgery, etc. The third section covers transfusion transmitted infections, while section four describes alternative strategies to allogenic blood transfusion. The last section speculates over immunomodulatory effects of blood transfusion.

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