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EDITORIAL

Hemoglobin optimization and transfusion strategies in patients undergoing cardiac surgery

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Abstract

Although red blood cells (RBCs) transfusion is sometimes associated with adverse reactions, anemia could also lead to increased morbidity and mortality in high-risk patients. For these reasons, the definition of perioperative strategies that aims to detect and treat preoperative anemia, prevent excessive blood loss, and define "optimal" transfusion algorithms is crucial. Although the treatment with preoperative iron and erythropoietin has been recommended in some specific conditions, several controversies exist regarding the benefit-to-risk balance associated with these treatments. Further studies are needed to better define the indications, dosage, and route of administration for preoperative iron with or without erythropoietin supplementation. Although restrictive transfusion strategies in patients undergoing cardiac surgery have been shown to effectively reduce the incidence and the amount of RBCs transfusion without increase in side effects, some high-risk patients (*e.g.*, symptomatic acute coronary syndrome) could benefit from higher hemoglobin concentrations. Despite all efforts made last decade, a significant amount of work remains to be done to improve hemoglobin optimization and transfusion strategies in patients undergoing cardiac surgery.

Key words: Cardiac surgery; Blood transfusion; Anemia; Transfusion threshold; Risk factor

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Core tip: Anemia and red blood cells transfusion are common during cardiac surgery, and could be associated with adverse reactions. Preoperative hemoglobin optimization through the identification and treatment of anemia and the definition of standardized transfusion algorithm using restrictive transfusion triggers play a central role in the development of Patient Blood Management programs. However, further researches are needed to better define transfusion triggers, based on pathophysiological indices, rather than single hemoglobin thresholds.

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INTRODUCTION

Patients undergoing cardiac surgery are at increased risk of excessive perioperative bleeding, and increased blood product transfusions[1]. Although blood products are safer than ever, transfusion of allogeneic blood products remains associated with a significant incidence of adverse reactions[2]. Last decades the development of Patient Blood Management (PBM) programs improved perioperative management, and decreased the use to blood products through a better identification of both patient-related and procedure-related risk factors[3].

On the one hand, cardiac surgery is among major procedures that significantly influence the distribution of body fluid through the large volumes of fluid administered during cardiopulmonary bypass (CPB), the volume of cardioplegia, and the amount of fluid administered to optimize cardiac output. In addition, the contact between blood and non-endothelial surfaces will lead to the "activation coagulopathy"[4], and all these mechanisms are part of the CPB-induced coagulopathy that significantly influences the requirement for blood products transfusion[5].

On the other hand, with the progress made in medical therapies and interventional cardiology, patients requiring cardiac surgery become older, and arrive to surgery with a huge number of comorbidities, and medications[6]. Patients are usually treated with antiplatelet agents and/or anticoagulants, which will increase the bleeding risk[7]. Although RBCs transfusion could be associated with adverse events; anemia in high-risk patients could also be associated with increased morbidity and mortality[8]. For these reasons, the definition of perioperative strategies that aims to detect and treat preoperative anemia, prevent excessive blood loss, and define "optimal" transfusion algorithms are crucial.

PHYSIOLOGY

Oxygen is major component of cellular homeostasis; the maintenance of an aerobic metabolism through adequate oxygen supply to cells is crucial. Cardiac output and the arterial oxygen concentration (CaO_2) will allow the maintenance of an adequate oxygen delivery (Do_2).

$Do_2 = CO \times CaO_2$, where $CaO_2 = (Hb \times SaO_2 \times 1.39) + (PaO_2 \times 0.0031)$

With SaO_2 corresponding to the arterial oxygen saturation, PaO_2 is the partial arterial pressure in oxygen, 0.0031 is the amount oxygen diluted in plasma, and 1.39 the amount of oxygen linked to 1 g of hemoglobin. Based on this formula, it appears evident that the hemoglobin concentration will play a central role in oxygen transportation throughout the body, and organs.

The adequacy of tissue oxygenation depends on tissue/organ metabolic needs. Tissue oxygenation is adequate when oxygen delivery (Do_2) is at least equal to the rate of oxygen consumed by the tissues (Vo_2: oxygen consumption). The ratio between Do_2 and Vo_2 allow for the determination of the oxygen extraction (O_2 ER), which in physiologic condition correspond to 25%-30% of the oxygen delivery. Interestingly, adaptive mechanisms allow the maintenance of adequate oxygen consumption in the presence of decreased oxygen delivery through an increase in the amount of oxygen extracted by the tissues[9]. Below a certain Do_2 level, the extraction could not be increased and metabolism will be shift to anaerobic metabolism. This change in metabolic characteristics will be associated with increased lactate plasmatic concentration, if prolonged may cause tissue damage[10].

Although a certain degree of anemia could be tolerated, the "critical" hemoglobin level that will not allow the maintenance of an adequate oxygen delivery will depend on different factors that include physiologic status (*e.g.,* sepsis increases oxygen demand) or condition (*e.g.,* anesthesia decreases oxygen demand)[11]. In case of acute and severe anemia, adaptive mechanisms to optimize the balance between oxygen supply and demand are regulated by hypoxia-inducible factors, and included neuronal nitric oxide synthase, erythropoietin, and hypoxia-inducible factors[12]. Although all these mechanisms improve oxygen delivery, organs with higher baseline oxygen extractions, such as the heart, are usually flow-dependent, which is obtained by vasodilatation of the coronary arteries[13]. This will have an important impact in patients suffering from coronary artery disease, and perioperative management of anemia in patients undergoing coronary artery bypass graft (CABG) surgery is crucial[14].

PREOPERATIVE OPTIMIZATION OF HEMOGLOBIN CONCENTRATION

Based on the World Health Organization (WHO), anemia is defined by hemoglobin levels < 12 g/dL in women, and < 13 g/dL in men[3]. If 25% of the general population is anemic, preoperative anemia is reported in 22% to 30% of patients undergoing cardiac surgery[15] Although preoperative anemia was associated with an increased incidence of acute kidney injury and strokes, both short and long-term mortality increased in anemic patients undergoing CABG surgery[16]. In addition, adverse events associated with hemorrhage, and blood product transfusion was higher in patients with preoperative anemia compared to non-anemic patients[17]. As a consequence, preoperative detection of anemia, and optimization of hemoglobin level is crucial.

Iron deficiency has been shown to be responsible of 29% of the preoperative anemia, followed by the presence of chronic kidney disease in 10.7%[18]. In case of iron deficiency, preoperative iron supplementation should be recommended. In patients undergoing cardiac surgery, Piednoir *et al*[19] reported that on 100 patients undergoing cardiac surgery, 37% had preoperative iron deficiency, from those one third were anemic. The authors also reported that 62% of patients with iron deficiency received RBC transfusion compared to 35% in controls[19]. No study assessed the efficacy of preoperative iron supplementation in patients undergoing cardiac surgery. So far, our experience is based on studies performed in colorectal[20] or orthopedic surgeries[21] that reported a significant reduction in RBCs transfusion in patients that received preoperative oral iron administration. Other authors reported that iv iron administrated within 3-5 wk before orthopedic surgery could significantly increase hemoglobin level[22]. Although a recent meta-analysis reported a significant increase in hemoglobin level, and reduction of RBCs transfusion following the iv administration of iron, this benefit was balanced by an increased incidence of infection. Based on current evidence, oral iron administration (200-300 mg/d) should be recommended in patients with preoperative iron deficiency, while iv supplementation (1000 mg weekly during 3-5 wk) might only be considered in case of contraindication to oral administration or short delay before a surgery that could not be postponed[23].

If the preoperative administration of erythropoietin stimulating agent could be attractive, the benefit-to-risk balance associated with preoperative administration of erythropoietin (EPO) remains weakly studied. Currently, EPO is approved in anemic patients without nutritional deficiency undergoing orthopedic surgery. However, its administration in patients undergoing cardiac surgery is currently prohibited due to an increased incidence of thromboembolic complication reported in pilot studies[24].

RESTRICTIVE *VS* LIBERAL TRANSFUSION TRIGGERS?

Transfusion has been used for years to increase hemoglobin concentration, and oxygen delivery. However, RBCs transfusion is associated with several side effects, and sometimes, increased mortality[25]. On the other hand, anemia has been associated with adverse outcomes ranging from cardiovascular events, heart failure, renal failure, prolonged recovery, and late mortality. Although the safety of blood products transfusion has been extensively enhanced last decades, there are still concerns over the hazards of transfusion, particularly with respect to the high rate of annual consumption of blood products worldwide (around 85 million units)[26]. With regard to complications associated with blood product transfusion, non-infectious risks such as human errors, acute hemolytic and non-hemolytic reactions have overpassed the risk of infection. Based on large studies performed in cardiac patients, blood product transfusion is associated with negative outcomes such as cardiac, pulmonary, renal, and neurologic complications, as well as increased length of hospital stay and death[27]. In addition, these side effects will have a significant impact on health care resource utilization.

As far as the 1990s, Bracey *et al*[28] reported that restrictive transfusion strategies (Hb threshold = 8 g/dL) led to a 20% reduction of RBCs transfusion without increase in the incidence of side effects[28]. However, it took about 10 years before the publication of a second prospective randomized study that compared a restrictive (hematocrit > 24%) *vs* liberal (hematocrit > 30%) transfusion strategy in patients undergoing cardiac surgery[29]. In this study, Hajjar *et al*[29] reported that although the restrictive transfusion strategy was associated with lower intra-operative hemoglobin levels, no difference was observed in term of morbidity and mortality. A Cochrane systematic review of 17 cardiac and non-cardiac trials published in 2010 concluded that restricted transfusion strategy decreases transfusion without increasing adverse outcomes such as cardiac events, thromboembolic complications, and death[30]. However, this review denotes that patients with "serious heart disease" should not be treated in this way. In a recent systematic review with meta-analysis, Curley *et al*[31] reported that only a few studies (n = 7) adequately compared the efficacy and safety of a restrictive transfusion protocol to a liberal approach in patients undergoing cardiac surgery. Although restrictive transfusion strategies significantly reduced the incidence of RBCs transfusion without side effect, the inter-studies variability was important, and further adequately powered studies are needed to assess the appropriate transfusion threshold in the cardiac population.

Based on a pathophysiologic decrease in anemia tolerance in patients with coronary artery disease, perioperative anemia could be associated with poor outcomes, and a specific transfusion strategy could probably be adopted in this high-risk population[14]. In 2013, Carson *et al*[32] published the preliminary results of a prospective randomized multi-center study that aimed to compare a restrictive (Hb > 8 g/dL) *vs* a liberal (Hb > 10 g/dL) transfusion strategy in patients with symptomatic coronary artery disease. The preliminary analysis reported that higher transfusion thresholds were associated with better outcome in this particular population. Recently, Murphy *et al*[33] published the results of a prospective

Table 1 Practice guidelines for red blood cell transfusion

Guidelines	Release date	Hemoglobin threshold definition	Level of evidence
Society of Thoracic Surgeons/Society of Cardiovascular Anesthesiologists[33]	2011	6 g/dL preoperative and on CPB	2C
		7 g/dL postoperative and at risk of ischemia on CPB	2C
British Committee for Standards in Haematology[34]	2012	7 g/dL stable, non-bleeding CAD	C
		8-9 g/dL ACS	
The American Association of Blood Banks[35]	2012	7-8 g/dL in stable patients	1A
		8 g/dL in patients with CVD	2B
		No number for ACS	Uncertain recommendation; very low-quality evidence
European Society of Anesthesiology[36]	2013	7-9 g/dL in bleeding patients	1C
American Society of Anesthesiologists[37]	2015	No number	-

1A: Strong recommendation, high quality evidence; 1B: Strong recommendation, moderate quality evidence; 1C: Strong recommendation, low quality evidence; 2A: Weak recommendation, high quality evidence; 2B: Weak recommendation, moderate quality evidence; 2C: Weak recommendation, low quality evidence; CPB: Cardiopulmonary bypass; CAD: Coronary artery disease; CVD: Cardiovascular disease; ACS: Acute coronary syndrome.

multicenter randomized study (TITRe2 study) that randomized more than 2000 patients undergoing cardiac surgery to a restrictive (Hb threshold < 7.5 g/L) or a liberal transfusion strategy (Hb threshold < 9 d/dL). Interestingly, the authors didn't observe any differences in term of postoperative outcome, mortality, and costs between the two transfusion strategies. The authors concluded that restricted strategy was not superior to a liberal transfusion strategy with respect to morbidity and health care costs. These results confirmed that indication for RBCs transfusion in patients undergoing cardiac surgery might not be guided by a single transfusion threshold and that some patients may benefit from higher hemoglobin level, while other may tolerate lower hemoglobin concentrations.

Recent guidelines emphasized that recommendations on blood transfusion in patients with cardiovascular disease are not supported by strong evidence[26,34-37]. (Table 1) Despite their differences, guidelines generally agreed that RBCs transfusion should not be recommended in case of hemoglobin concentration ≥ 10 g/L and might be useful in case of hemoglobin concentration < 7 g/L[38]. However, transfusion triggers might be reconsidered in critical scenario, and especially in bleeding situations[26,34-36]. Evidence is particularly limited in clinical contexts such as acute coronary syndrome, where the recommendation for higher hemoglobin threshold is still controversial[26]. Patients with acute coronary syndrome (ACS) or patients who were at risk of end organ ischemia were included in different clinical trials over the past years, but the relationship between ACS, RBCs transfusion, and outcome remains to be determined[26,37]. Further results are waited in this context, but this supports the hypothesis that one single transfusion threshold could not fit to all patients, and that RBCs transfusion should be based on more than a single hemoglobin measurement.

CONCLUSION

Both anemia and transfusion are associated with adverse events and increased morbidity in patients undergoing cardiac surgery. Although the "optimal" RBCs transfusion strategy has not yet been defined, RBCs transfusion should be preferred when its benefits outweigh the risks. Patients with cardiac diseases are more vulnerable to anemia-related hypoxia, and recent data suggested that a restrictive transfusion strategy was not superior to a liberal transfusion, that could be associated with "better" outcome in some high-risk patients with symptomatic coronary artery disease. Each cardiac surgical department might develop standardized transfusion algorithm, based on a multidisciplinary approach. This approach should include preoperative identification of anemic patients, preoperative measures to increase hemoglobin concentration (*e.g.,* iron and/or erythropoietin), intraoperative measure to decrease blood loss, and definition of "optimal" transfusion trigger based on patient's characteristics, rather than a single hemoglobin threshold. Because on current knowledge the "ideal" transfusion thresholds to be recommended in cardiac patients is not yet known, further large prospective studies are urgently needed to determine the efficacy and safety of different transfusion strategies in this high-risk population.

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