

## Review

# Patient Blood Management: Anesthesiologist's Perspectives

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Preoperative anemia should be diagnosed and treated before surgery, because anemia is associated with increased postoperative mortality and morbidity. Even if iron deficiency is not detected, the possibility of functional iron deficiency should be considered. During surgery, patients should be managed to avoid hypothermia, acidosis, and hypocalcemia, while maintaining adequate blood pressure and preventing dilutional coagulopathy. It is currently recommended to start transfusion when hemoglobin is under 7–8 g/dL in patients without cardiac problems, using restrictive strategy rather than liberal, due to dangers of complications from transfusion. For those who refuse transfusion, or when transfusion is difficult due to multiple antibodies, or when attempting to reduce allogeneic transfusion, preoperative autologous blood donation (PAD), intraoperative acute normovolemic hemodilution (ANH), intraoperative blood salvage, or postoperative blood salvage can be used. For patients with trauma or massive bleeding, damage control resuscitation of permissive hypotension, restriction of crystalloid infusion, transfusion of blood product in a ratio similar to whole blood (1:1:1 of FFP, platelets, PRBC) must be actively carried out.

**Key words:** Anemia; Blood transfusion; Intraoperative blood salvage; Postoperative blood salvage

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## INTRODUCTION

Blood transfusion is generally considered to be the solution of anemia and blood loss during surgery. Transfusion is a very efficient and effective method to correct anemia, but there has been increasing evidence that blood transfusion does not lead to improved outcomes and that morbidity and mortality increase in a dose-dependent manner [1,2]. It has been shown that even a single unit of transfused packed red blood cells (PRBCs) can increase 30-day mortality, complicated mortality, pneumonia and sepsis [3]. Therefore, it is preferable to avoid unnecessary blood transfusion or to minimize blood transfusion. In surgical patients, patient blood management focuses on anemia management, minimization of blood loss, appropriate transfusion for reducing surgical risk, and improving patient outcome after surgery. Recognition and manage-

ment of pre-operative anemia represent an opportunity to optimize patient status before surgery, thereby reducing blood transfusion and potentially improving recovery from surgery and associated postoperative outcomes. A complex approach such as anesthetic strategy and operative techniques, pharmacological intervention, and cell salvage is required to reduce bleeding during surgery. In this review, we reviewed the studies about blood management in the stance of anesthesiologists. Management of coagulopathy and blood component therapy was not included in this review.

## PRE-OPERATIVE PERIOD

Mild anemia before surgery can increase complications by 30–40%, and the degree of complication is proportional to the degree of anemia [4,5]. The World Health Organization defines anemia as he-

hemoglobin concentration below 11.0 g/dL for children aged 6 months to 4 years old, 11.5 g/dL for children aged 5 to 11 years old, 12.0 g/dL for children from 12 years old and for non-pregnant women who are 15 years and older, 11 g/dL for pregnant women, and 13.0 g/dL for men who are 15 years and older [6,7]. It is necessary to diagnose the cause of anemia in patients scheduled for surgery to treat anemia. Anemia can be treated by transfusion before surgery to increase hemoglobin. However, this cannot be a fundamental treatment for anemia, and the risk of complications from transfusion is still present [1,8]. To optimize patients before surgery and reduce the need for transfusion during operation, it is recommended that hematologic function be measured 30 days prior to major surgery to find the cause of anemia and to treat the cause [9]. This leaves adequate time to investigate and manage diagnosed anemia without resorting to blood transfusion or delaying surgery. Patients may have anemia due to malnutrition, blood loss, or combination of these. Anemia may also be caused by chronic diseases (renal failure, gastrointestinal disease, hemoglobinopathies and chronic inflammation). Functional iron deficiency may be caused by iron-restricted erythropoiesis in the presence of normal or increased amounts of stored iron [10]. In case of iron deficiency anemia, iron supplements can be administered orally or intravenously [11,12]. Oral iron supplements are inexpensive and easy to use. However, they can induce absorption disturbance or side effects such as gastrointestinal disturbance, abdominal pain, diarrhea, or constipation. Also, oral iron supplements would need some time—weeks or months—until optimal effect shows. A systematic review has demonstrated that oral iron ingestion may reduce the proportion of patients requiring transfusions [13]. However, some studies have shown no significant differences in demand of transfusion during the perioperative period between those who were administered oral or intravenous iron supplements and those who were not [14-16]. About this, American Society of Anesthesiologists (ASA) Practice Guidelines for perioperative blood management judged as it is equivocal whether administration of iron supplements reduce transfusion during perioperative period or not [17]. Intravenous iron could be used when there is infection, when oral iron is difficult to use due to side effects, and when there is not enough time until operations. Intravenous iron should be injected at least 10 days before surgery for its effectiveness, and maximal effectiveness shows at 2 to 4 weeks after injection [18].

Recombinant erythropoietin (EPO) is being used to stimulate erythropoiesis in patients who need dialysis. According to meta-analysis, erythropoietin with or without iron is effective in reducing the number of allogeneic transfusions as well as reducing the amount of allogeneic transfusions [19-21]. However, practical use

of EPO is not encouraged by recent National Institute for Health and Care Excellence (NICE) guidelines, except for those who refuse blood transfusion or when blood transfusion is unavailable due to red cell antibodies [22]. EPO is not only expensive but has also been linked to increased risks of thromboembolic events and tumor growth through the promotion of angiogenesis [22,23].

If the hemoglobin level is sufficient in a patient who is expected to be transfused during or after the surgery, preoperative autologous blood donation (PAD) can be used to preserve autologous blood before surgery and transfuse it when needed. PAD is useful in patients who refuse allogeneic blood transfusions in elective surgery where more than 4 units of transfusion are anticipated, patients with rare blood types, and patients who are difficult to find suitable blood due to various antibodies [24,25]. PAD can reduce risks of transfusion-related infections, alloimmunization, and transfusion-related acute lung injury (TRALI) compared to allogeneic blood, but there are still risks of clerical error, transfusion-associated circulatory overload (TACO) and bacterial infection. PAD is most effective when erythropoietin is administered together [26-28]. Because it is not effective in those without iron deficiency, iron supplements need to be administered before PAD for those with iron deficiency [26,29].

## INTRA-OPERATIVE AND POST-OPERATIVE PERIOD

### 1. Physiologic compensation

Blood transfusion is often necessary during surgery and complications following blood transfusion may occur. In order to minimize blood transfusion, anesthesiologists should determine when to start transfusion, how much blood is to be administered, and what hemoglobin levels to be targeted in the context of bleeding. The patient's condition, how well the patient is compensated for bleeding, and the type of operation are also important factors in determining transfusion.

When bleeding occurs, the compensation mechanism works for anemia through the increased cardiac output, reduction in systemic vascular resistance with vasodilation of the vessels to the major organs, and an increase in tissue oxygen extraction [30-32]. In patients with bleeding, the goal of treatment is to maintain normal intravascular volume, cardiac output, and organ perfusion. Intravascular volume and cardiac output can be maintained by administering fluids, but normovolemic dilutional anemia can occur. Mathru and colleagues reported that the oxygen supply and consumption to the splanchnic and preportal area were inadequate when the hemoglobin decreased to 5.9 g/dL in normovolemic anemia [33]. This

is because there is a limit to increasing oxygen supply to tissue just by the fluid administration. Ultimately, hemoglobin which carries oxygen to the tissue has the main role in organ perfusion. The reason for transfusion is to prevent tissue hypoxia by supplying oxygen to the tissue through transfused hemoglobin, eventually improving oxygen carrying capacity. If acute or chronic anemia occurs, compensation for alleviating anemia operates. Depending on the patient's cardiovascular reserve, there are patients who can tolerate low hemoglobin levels and others who cannot. It is unclear whether increasing hemoglobin levels can further improve tissue oxygenation when the patient has stable anemia that can be compensated for anemia. However, at the stage where all compensation fails, improper oxygen supply causes ischemia and injury leading to tissue hypoxia, multiple organ failure, and death [34]. Although there is a recent emphasis on minimizing blood transfusions, clearly a hemoglobin level below which a blood transfusion should be given exists.

## 2. Liberal vs. restrictive transfusion strategy

Liberal versus restrictive transfusion strategy is based on the hemoglobin level when a transfusion decision is made. A restrictive strategy is to transfuse only when the hemoglobin level is below 7–8 g/dL. In contrast, a liberal strategy is to transfuse when the hemoglobin level is below 9–10 g/dL. Many studies comparing restrictive and liberal transfusion strategies have found no significant differences in mortality, cardiac, neurologic or pulmonary complications, and length of hospital stay [35–43], even though the restrictive-strategy group received much less transfusion than the liberal-strategy group [35–39]. Through these studies, over the past decade, transfusion management has shifted from a liberal to a restrictive strategy with careful consideration of the balance between the risk of transfusion and the physiologic compensation of anemia. Recently, ASA Practice Guidelines for perioperative blood management defined 'restrictive' as blood transfusion at less than 8 g/dL hemoglobin and less than 25% hematocrit and recommended that a restrictive transfusion strategy be used safely to reduce blood transfusion [17]. The determination of whether hemoglobin concentrations between 6 and 10 g/dL justify or require a red blood cell transfusion should be based on potential or actual ongoing bleeding (rate and magnitude), intravascular volume status, signs of organ ischemia, and adequacy of cardiopulmonary reserve [17]. The transfusion trigger probably should be different in older patients with coexisting conditions who have abnormal cardiovascular status. Clearly, patients with active bleeding, especially those with cardiovascular disease, should be subjected to a more liberal transfusion strategy [44].

## 3. Blood conservation strategy

Acute normovolemic hemodilution (ANH) and intraoperative blood salvage can be used as blood conservation strategies during surgery.

ANH is a procedure that removes the patient's whole blood prior to surgical incision, collects it in a blood bag containing anticoagulants, places it at room temperature, and then reinfuse it to the patient at the end of surgery, when no further bleeding is expected, or when transfusion is needed. While the blood is being collected, normovolemia is achieved by administration of either 3 mL of crystalloid or 1 mL of colloid solution for each 1 mL of blood withdrawn [27]. The biggest advantage of ANH is that red blood cell loss decreases when bleeding occurs during surgery due to low hematocrit [45]. Target hematocrit of ANH is usually 25–30% although it depends on the patient [27]. The simple formula for allowable blood loss is used to calculate the volume to be removed. The formula is as follows.  $\text{Volume to be removed} = \text{EBV} \times [(\text{Hct}_i - \text{Hct}_t) / \text{Hct}_{\text{ave}}]$ , where EBV is the estimated blood volume;  $\text{Hct}_i$ , the initial hematocrit;  $\text{Hct}_t$ , the target hematocrit;  $\text{Hct}_{\text{ave}}$ , the average hematocrit [27,46]. In a clinical study, when minimal ANH (representing  $\leq 15\%$  of patients' blood volume) was conducted, it was possible to save RBC 100 mL which are about 0.5 unit of PRC [47]. More blood will be saved if moderate hemodilution (target hematocrit levels of 28%) is conducted. Although some reports have shown that ANH was as effective as PAD [48–50], there are also reports that the need for allogeneic transfusion had not been significantly reduced [27,46,51]. Because blood collected by ANH is stored at room temperature and is usually returned to the patient within 8 hours of collection, deterioration of platelets or coagulation factors is minimal. Withdrawal of whole blood and replacement with crystalloid or colloid solution decrease arterial oxygen content, but compensatory hemodynamic mechanisms and the existence of surplus oxygen delivery capacity make ANH safe. A sudden decrease in RBC concentration reduces blood viscosity, thereby decreasing peripheral resistance and increasing cardiac output. If cardiac output can be effectively compensated, oxygen delivery to the tissues at a hematocrit of 25% to 30% is as good as, but no better than, oxygen delivery at a hematocrit of 30% to 35% [52]. The contraindications to ANH include preoperative anemia, significant cardiopulmonary comorbidities such as uncontrolled hypertension, aortic stenosis or recent myocardial infarction or cerebral vascular accident, or active infection.

Intraoperative blood salvage has the advantage of reducing allogeneic blood transfusion by collecting blood that is suctioned during surgery and then administering it to the patient [27,28,46,53]. Using a device, suctioned blood is washed with saline and then

centrifuged. This process provides saline-suspended red blood cells with about 50–60% of hematocrit. MacIvor and colleagues reported that intraoperative salvage can reduce allogeneic blood transfusion as much as PAD and that it showed greater hemoglobin level after surgery [54]. Adverse effects of intraoperative blood salvage have been reported, including air embolism [55], hemolysis of salvaged blood [56], higher plasma-free hemoglobin levels, and bacterial contamination [57]. Blood that has been aspirated from the surgical field may have bacterial or tumor cells, so re-administration to the patient may be dangerous. However, microbiologically contaminated blood—even though not undergoing a proper washing phase—did not increase the risk of postoperative infection or positive culture [58,59].

Postoperative blood salvage can be tried after surgery. This method is re-administration of blood collected through the surgical drain. There are two ways for this method. One way is the same with intraoperative blood salvage—blood is washed and concentrated by centrifugation. The other way is to reinfuse the blood after filtering it twice, once through a 100 to 200  $\mu$ m filter to remove large debris and fibrin, then through the standard 40  $\mu$ m filter to collect micro-aggregates [60].

Recent Cochrane review [61] reported that there was no increase in mortality, reoperation for bleeding, infection, wound complications, non-fatal myocardial infarction, thrombosis, risk of stroke or length of hospital stay due to intraoperative or postoperative blood salvage, but rather a decrease in infection and wound complications. Additional hemostatic therapies (such as platelets or fresh frozen plasma) may be required because retransfused washed RBCs from cell salvage provide no plasma, clotting factors, or platelets.

#### 4. Massive transfusion

If there is massive bleeding during surgery, close communication between surgeons, anesthesiologists, and nurses is essential. Trauma-induced coagulopathy occurs due to dilutional coagulopathy (due to infusion of crystalloids and transfusion of RBC products), hypothermia, acidosis resulting from tissue hypoxia, activation of inflammatory mediators, and fibrinolysis and thrombocytopenia by trauma. Therefore, it is important to limit fluid, prevent hypothermia, and maintain blood pressure and blood flow to prevent acidosis. In case of massive bleeding, it is recommended that FFP (fresh frozen plasma), platelets, and PRBC (derived from the military setting) be administered at the golden ratio. In a recent PROPPR trial [62], there was no statistically significant difference in mortality at 24 hours and 30 days between the two groups after 1:1:1 or 1:1:2 administration of FFP, platelets, and PRBC. However, more patients in

the 1:1:1 group achieved hemostasis, and fewer died due to exsanguination by 24 hours.

Standardized approach through massive transfusion protocols prepared for the management of massive bleeding is important for systematic blood ordering, blood transfusion, blood testing, and patient care.

## CONCLUSION

Perioperative patient blood management focuses on minimizing bleeding, maintaining normal physiology, and reducing blood transfusion demands. This includes measuring anemia before or after surgery, optimizing hemoglobin and iron store, pre-intervention of bleeding risk, using hemostatic agents, autologous blood salvage, etc. Restrictive strategy is preferred to liberal strategy, but clinical factors of patients should be considered.

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