

# Optimal management of perioperative anemia: current perspectives

Jad Bou Monsef<sup>1</sup>  
Friedrich Boettner<sup>2</sup>

<sup>1</sup>Orthopaedic Surgery Department, University of Illinois at Chicago, Chicago, IL, <sup>2</sup>Adult Reconstruction and Joint Replacement Service, Hospital for Special Surgery, New York, NY, USA

**Abstract:** Anemia is prevalent in surgical patients and is associated with increased morbidity and mortality. Allogeneic blood transfusions have long been the first choice in addressing the perioperative anemia in surgical patients. Such transfusions have been shown to adversely influence clinical outcome, prolong hospital stay, and increase complications and costs. Evidence of benefit from red blood cell (RBC) transfusion is hard to find, and most benefit from RBC transfusion is assumed and not scientifically proven. As such, perioperative anemia bears a significant clinical and economic impact on the health care landscape. Blood management relies on sustainable and cost-efficient interventions individualized to each patient and risk level. Restrictive transfusion triggers coupled to a multimodal strategy for reducing blood loss should be adopted as the standard of care in surgical patients. The approach aims at optimizing patient preoperative status and RBC stock as well as minimizing perioperative blood loss.

**Keywords:** blood management, allogeneic, autologous, transfusion, erythropoietin, tranexamic acid, reinfusion, surgery

## Introduction

Anemia is common in patients undergoing surgery and is reported in up to one out of four patients preoperatively.<sup>1-6</sup> The percentage of anemic patients increases postoperatively, not only secondary to surgical blood loss but also from the ensuing systemic inflammatory response that in turn inhibits erythropoiesis and creates a state of functional iron deficiency despite normal iron stores.<sup>7,8</sup> Anemia is associated with increased risk of adverse outcomes, longer hospital stay, and higher morbidity and mortality.<sup>9-11</sup> Even mild anemia was shown to increase relative risk of adverse events by 30%–40%.<sup>11</sup> It is also the major predictor of the need for transfusion of allogeneic blood.<sup>12</sup> Other factors such as age, sex, and body mass index contribute to perioperative risk of transfusion.<sup>13</sup> Risks of allogeneic transfusion are rare but can be life threatening. One of the most devastating risks of allogeneic blood is clerical error, which takes place in 1:20,000–24,000 transfusions.<sup>14</sup> Inherent risks of allogeneic transfusions persist in the form of an increased susceptibility and transmission of infections, transfusion reactions, altered immune response, circulatory overload, and transfusion-related acute lung injury.<sup>15,16</sup> Therefore, blood transfusions are independently associated with surgical complications, infections, poorer function and recovery, and overall increased mortality, hospital stay, and costs.<sup>10,17-20</sup>

A growing awareness of the risks of perioperative anemia and blood transfusion has highlighted the need for comprehensive blood management in surgical patients. Blood management is a multimodal approach that relies on three pillars: optimizing

Correspondence: Friedrich Boettner  
Adult Reconstruction and Joint  
Replacement Service, Hospital for Special  
Surgery, 535 East 70th Street,  
New York, NY 10021, USA  
Tel +1 212 774 2127  
Email boettnerf@hss.edu

erythropoiesis, minimizing perioperative blood loss, and optimizing the patient-specific physiological reserve of anemia.<sup>21</sup> The World Health Organization (WHO) has recognized the importance of perioperative blood management (World Health Alliance resolution A 63.12) and has urged all member countries to adopt it as standard of care.<sup>22</sup> This primarily advocates going beyond the concept of appropriate use of blood and addressing modifiable risk factors that increase the risk of transfusion before the need arises for one.<sup>23</sup> The move to adopt patient blood management is driven not only by the lack of efficacy and safety of current transfusion practices but also by their direct and indirect costs and the burden on health care resources.<sup>24,25</sup> Blood management relies on sustainable and cost-efficient interventions individualized to each patient and risk level. It has been identified as one of the ten overlooked opportunities for significant performance improvement and cost savings for hospitals and health systems.<sup>26</sup> Blood management options encompass the preoperative workup and optimization, the surgery itself, and the postoperative period.

## Preoperatively

Anemia is defined by the WHO as having hemoglobin (Hb) <13 g/dL in men, <12 g/dL in nonpregnant women, and <11 g/dL in pregnant women, with ~1.26 billion people affected worldwide.<sup>27</sup> Identifying patients at risk of requiring transfusions and optimization of their Hb level is key to reduce blood loss and transfusion requirements, and to decrease morbidity and mortality in the perioperative period. The workup includes the detection, evaluation, and treatment of anemia prior to the surgery, as well as the optimal management of medical conditions or medications that may interfere with coagulation and bleeding. The main causes of anemia in the general population are iron, folate, and vitamin B12 deficiency, hemoglobinopathies, and renal failure. This may be compounded by the condition for which the patient is undergoing surgery. Preoperative blood management options aim at optimization of blood stores and include iron supplementation, use of erythropoiesis-stimulating agents (ESAs), and preoperative autologous blood donation (PABD).

## Iron and ESAs

Preoperative iron has shown benefits in both anemic and nonanemic patients.<sup>28,29</sup> Since the mobilization of iron from ferritin stores is slow, iron supplementation is advocated even with normal ferritin levels.<sup>30</sup> Intravenous administration is significantly more effective in inducing the erythropoietic response,<sup>31</sup> and is of particular use in patients with anemia

of chronic disease.<sup>30</sup> Such patients do not typically respond to oral iron due to impaired intestinal absorption and the increased sequestration of iron in macrophages.<sup>32</sup> Several studies and meta-analyses have established the efficacy of intravenous iron in increasing Hb levels and reducing transfusion rates, including in patients on dialysis.<sup>33–36</sup> Intravenous iron is a safer alternative to blood transfusion,<sup>28</sup> and its effect is more pronounced when coupled with ESAs.<sup>35,37</sup> Side effects are usually mild and include anaphylaxis, which is less common with the newer formulations.

The erythropoietic response is physiologically triggered by blood loss in surgery, with erythroid hyperplasia visible after 3–6 days and reaching maximal response in 7–10 days.<sup>38</sup> ESAs are effective at increasing Hb levels by the equivalent of 1 unit of blood per week, given adequate iron supplementation. Several studies have supported the effectiveness of ESAs in decreasing the risk of transfusion in the perioperative setting with no reported increase in thromboembolic events.<sup>39–42</sup> The concern of the risk of thrombosis associated with ESAs was raised in trials where the incidence of venous thromboembolism was higher in the group that received preoperative ESA.<sup>43</sup> An important distinction is that the thromboembolic risks of ESAs were reported in trials with patients with chronic renal disease who received higher doses over longer time periods, as well as high-risk populations such as critically ill and cancer patients.<sup>44,45</sup> In contrast, preoperative ESA in elective surgery utilizes lower doses for shorter durations.<sup>46</sup> It is important to keep in mind that a higher risk of thromboembolic events might ensue from increased blood viscosity and platelet concentration. Erythropoietin (EPO) is contraindicated for patients with comorbidities that may predispose to adverse side effects, such as uncontrolled arterial hypertension, previous acute myocardial infarction or stroke, unstable angina, and severe carotid stenosis. The US Food and Drug Administration requires a warning to be added to the package inserts to urge the use of deep vein thrombosis (DVT) prophylaxis in surgical patients receiving EPO.<sup>47</sup> Monitoring Hb and hematocrit levels in all patients treated with EPO is indicated, as well as using low doses and setting lower target Hb levels. More common side effects include local skin irritation at the injection site, increased blood pressure, and headaches.<sup>48</sup> Several different dosing regimens of EPO are available, and iron supplementation is necessary in all cases. The most commonly used approaches are 300 IU/kg daily for 15 days, starting 10 days before surgery, or 600 IU/kg on preoperative days 21, 14, and 7 and on the day of surgery. The recommended dosage in cases of blood donation is 600 IU/kg (or a 40,000 IU vial)

twice a week. Treatment should be discontinued if Hb levels reach 15 g/dL. Blood levels of ferritin, folic acid, and vitamin B12 should be checked and corrected before initiating therapy.<sup>43,49–54</sup>

Patients with chronic conditions such as autoimmune or kidney disease need to be evaluated on an individual basis, as many of them would be in a state of functional iron deficiency. Chronic anemia from inflammation, infections, and malignancies is often mild to moderate. It is important to identify this type of anemia in which enteral iron supplementation has no therapeutic benefits due to sequestration in macrophages and enteric cells.<sup>32</sup> This can be overcome with the use of intravenous iron,<sup>30</sup> and higher doses of EPO may be required to trigger sustained erythropoiesis.<sup>55</sup>

### Preoperative autologous blood donation

PABD as a blood-saving modality in elective procedures offers advantages in terms of safety from infection transmission, early stimulation of erythropoiesis preoperatively, and the dilution of blood resulting in lower red blood cell (RBC) loss intraoperatively.<sup>56,57</sup> Iron supplementation with or without ESA therapy is key for adequate erythropoiesis. PABD has shown to reduce allogeneic transfusion requirements.<sup>5,58–60</sup> A Cochrane review as well as other large-scale studies showed significant reduction in exposure to allogeneic blood at the expense of a higher overall transfusion rate (allogeneic and/or autologous).<sup>1,61</sup> The cost efficacy of PABD may be optimized by restricting its use to anemic patients, thus significantly decreasing the number of units wasted.<sup>60,62</sup> Autologous blood donation may be of limited use when other blood-saving tools are used, such as hemostatic agents or cell salvage.<sup>63</sup> Autologous blood donation has not been associated with prolonged hospitalization or increased morbidity or mortality.<sup>64</sup> However, concerns limiting the widespread adoption of this technique include cost and number of wasted blood units, as well as the potential risks of transfusion reactions, bacterial contamination, and clerical errors. It is also time-consuming and requires a setup in place to adequately handle the blood units. The EPO response in some patients might be insufficient, exacerbating their anemia and increasing the risk of allogeneic transfusion.<sup>14</sup>

### Intraoperatively

Intraoperative anemia can be caused by acute blood loss as well as hemodilution as a result of fluid administration and hypotensive anesthesia. Intraoperative blood management measures rely on minimizing blood loss and recovering the lost blood. This is possible through hypotensive anesthesia

techniques, hemodilution, reinfusion devices, and pharmacologic antifibrinolytic agents.

### Hypotensive neuraxial anesthesia

Controlled hypotension is the reduction of the mean arterial pressure to 50–75 mmHg and has been shown to decrease postoperative wound drainage and intraoperative blood loss by up to 40%.<sup>65–67</sup> A meta-analysis has shown its benefit in orthopedic surgery,<sup>68</sup> and it has been associated with fewer perioperative blood transfusions,<sup>69,70</sup> a lower rate of DVT,<sup>71,72</sup> and a low perioperative mortality rate.<sup>73</sup> Although the technique has been used safely in patients with hypertension, ischemic heart disease, and in the elderly, it tends to be utilized in healthier patients due to fear of compromising organ perfusion. This technique also results in a cleaner surgical field. Of note, the volume expansion that goes along with deliberate hypotension may lead to a higher degree of hemodilution in the immediate postoperative period.<sup>74</sup> This could cause a false anemia and should be taken into consideration when interpreting Hb levels postoperatively.

### Acute normovolemic hemodilution

Acute normovolemic hemodilution (ANH) consists of extracting a certain blood volume from the patient and simultaneously exchanging for crystalloid and/or colloid solution to maintain normovolemia.<sup>75</sup> The concept is to effectively create a well-tolerated intraoperative anemia and dilute the blood lost in surgical procedures with significant anticipated blood loss such as major cardiac, orthopedic, thoracic, or liver surgery. The activity of coagulation factors and platelets is maintained in the stored blood.<sup>15</sup> The autologous whole blood is transfused at the end of the procedure and provides red cells, fresh clotting factors, and platelets. As long as normovolemia is preserved, stroke volume and cardiac output increase with no change in heart rate as a result of increased venous return, peripheral vasodilation, and rightward shift of the Hb dissociation curve.<sup>76</sup>

The technique is similar to PABD, except that it does not require the same logistic setup and is possible in nonelective situations. In a systematic review of its use in different types of surgical procedures (cardiac, hepatic, urologic, and orthopedic), ANH showed a 55% reduction in the risk of receiving allogeneic blood as well as a reduction in number of allogeneic units transfused by 2.8 units per patient.<sup>77</sup> However, the review found that ANH offers no significant advantage when associated with a transfusion protocol.<sup>77</sup> As for the safety of this technique, two meta-analyses found no significant increase in morbidity (myocardial infarction,

myocardial ischemia, alteration of left ventricular function, DVT, stroke, hypotension, or transfusion reaction), postoperative infection, length of stay, or mortality.<sup>75,77</sup>

While ANH relies on restoring the blood volume with crystalloid and colloid, another approach is hypervolemic hemodilution utilizes crystalloid with no phlebotomy. The rationale for this approach is to dilute the blood lost during surgery. The advantage is that it does not involve any withdrawal of blood and is less time-consuming. The patients must be healthy enough with efficient physiological compensation mechanisms to tolerate acute anemia, and it is contraindicated in patients with coronary artery, renal, pulmonary, and hepatic disease. It has been reported to be comparable to normovolemic hemodilution in significantly reducing perioperative allogeneic blood requirements and cost.<sup>78</sup>

## Perioperative cell salvage

Intraoperative cell salvage involves the collection of drainage or suction blood and its reinfusion during or after the procedure.<sup>79</sup> Cell salvage systems are able to recover up to 60% of the blood lost using filtered or unfiltered cell savers<sup>56,80</sup> and therefore require ~750 mL of blood loss to salvage a unit of packed RBCs.<sup>77,80</sup> Cell savers are commonly used in cardiac, vascular, orthopedic, liver, and neurosurgical procedures and have been shown to reduce exposure to allogeneic blood by 38% and an average saving of 0.68 units of RBC per patient.<sup>81–83</sup> Similar to ANH, this modality has been reported to be of limited use when associated with a restrictive transfusion strategy.<sup>84</sup> It has not been associated with increased mortality or morbidity, and its contraindications include cancer, intraoperative contamination of the surgical field, and infection.<sup>77,85,86</sup> Of note, potential complications include the activation of intravascular coagulation with increased capillary permeability causing acute lung injury and renal failure. This is known as salvaged blood syndrome and is related to the dilution of salvaged blood from large quantities of saline solution which creates deposits of cellular aggregates. In addition, cell-salvaged blood contains no platelets or coagulation factors, and therefore, platelets, fresh-frozen plasma, and cryoprecipitate transfusions are required in cases of massive blood loss.<sup>87</sup>

## Hemostatic agents

Pharmacologic manipulation of the coagulation cascade through different mechanisms that inhibit fibrinolysis or promote coagulation is a major strategy for reducing surgical blood loss.<sup>88</sup> Hemostatic agents including antifibrinolytics,

desmopressin, recombinant factor VIIa, and fibrin sealants have been used to minimize bleeding in situations such as dental extraction, tonsillectomy, prostate surgery, heavy menstrual bleeding, and cardiac surgery, and in patients with hemophilia.

The antifibrinolytics tranexamic acid (TXA) and ε-aminocaproic acid are derivatives of the amino acid lysine. They prevent breakdown of blood clots by inhibiting the proteolytic activity of plasmin on fibrinogen as well as the production of plasmin from plasminogen. TXA is six to ten times more potent than ε-aminocaproic acid and has gained widespread use in recent years, namely in cardiovascular, trauma, and orthopedic surgery.<sup>15</sup> The use of TXA has shown significant reductions in blood loss and allogeneic blood transfusion requirements in an extensive review of >25,000 surgical patients.<sup>88</sup> TXA has been found to reduce bleeding and improve outcomes, including mortality. The use of TXA in major orthopedic procedures was associated with a reduction in blood loss by a mean of 126 mL intraoperatively and 408 mL postoperatively in a meta-analysis of 46 randomized controlled studies including 2,925 patients.<sup>89</sup> Additionally, the risk of transfusion was decreased by half, and the volume of blood transfused was reduced by a mean of 205 mL. No increase in the risk of thromboembolic events was detected. These results mirror previous meta-analyses reporting significant reduction in blood loss with the use of intravenous and topical TXA by 34% and 29%, respectively.<sup>90,91</sup> Similar results were observed in terms of transfusion rate and risk of thromboembolic events.<sup>92,93</sup> The reduction in postoperative transfusion rates remains the most clinically relevant measure of modalities that target surgical blood loss. TXA has been considered particularly useful in knee replacement as the application of a tourniquet leads to increased activation of local fibrinolysis, platelet dysfunction, venous stasis, and blood vessel wall damage.<sup>94</sup> Administered topically or intravenously, TXA can decrease blood loss, allogeneic transfusion risk, and volume of autologous blood transfused after total knee arthroplasty.<sup>95–97</sup> Both intravenous (single or repeated bolus dosing or continuous infusion) and topical (intra-articular) administration of TXA have been shown efficient in orthopedic surgery. Topical irrigation doses range from 500 mg to 3 g in up to 100 mL of saline and are left in contact for at least 5 minutes prior to wound closure. Intravenous doses used in clinical trials vary significantly, but the most commonly used dose is 10–15 mg/kg. This can be followed by an infusion of 1 mg/kg/h until after the surgery as it has a short half-life and is almost completely excreted within 24 hours.<sup>15</sup>

Fibrin sealants encompass a variety of topical agents to promote platelet aggregation or the coagulation cascade.



Collagen- or plant-based products such as gelatin sponges or compounds containing cellulose act passively by providing a physical structure for contact activation and promotion of platelet aggregation.<sup>98</sup> Active agents possess intrinsic biological activity and are topically applied biological adhesives that consist of human fibrinogen and thrombin mixed with calcium and serve to initiate the final stages of coagulation. Their hemostatic action is less susceptible to coagulopathies due to clotting factor deficiencies or platelet dysfunction.<sup>99</sup> They have been determined safe and efficient at reducing Hb drop, blood drainage volume, hematoma formation, and incidence of blood transfusion.<sup>100,101</sup> However, fibrin sealants are significantly less cost efficient than TXA or even autologous blood donation.<sup>60</sup> They also carry a theoretical risk of infection transmission as they are derived from human blood products. Among hemostatic agents, TXA has gained widespread use as cheap and widely available, with lower transfusion rates that reflect on early mobilization, length of stay, and cost.

## Postoperatively Surgical drains

Drains serve to avoid postoperative hematoma formation and the compression of vital structures. By increasing tension and decreasing perfusion, a hematoma could impair wound healing, provide a medium for infection, and cause pain and stiffness resulting in delayed rehabilitation and extended hospital stay.<sup>102,103</sup> However, drains may also provide a conduit for the entry of bacteria.<sup>104,105</sup> Ninety percent of the blood is collected within the first 24 hours after which the risk of retrograde infection surpasses any proposed benefit, and the drain should be discontinued.<sup>106</sup> Closed suction drainage in total joint arthroplasty was found to be associated with a 40% increase in blood transfusions when compared to controls.<sup>107</sup> It is possible to reinfuse less than 1 L of the blood from a wound drain, filtered or unfiltered, within 6 hours.<sup>108</sup> A Cochrane meta-analysis failed to detect a significant difference in the incidence of wound infection, hematoma, dehiscence, or reoperations between drained and undrained wounds in orthopedic patients.<sup>107</sup> More blood transfusions were associated with the use of drains, and more bruising and frequent dressing reinforcement in the control group. The review concluded that there was insufficient evidence to support the routine use of closed suction drainage in orthopedic surgery.<sup>14,102,103,107</sup>

## Transfusion threshold

Blood transfusion has been recognized as one of the most frequently performed and overused procedures by the American

Board of Internal Medicine, with a significant percentage of transfusions found to be inappropriate.<sup>109</sup> Transfusions do not address the underlying cause of anemia. An analysis of just under one million surgical patients reported that transfusion of a single unit of packed red cells increased the multivariate risk of mortality, wound problems, pulmonary complications, renal dysfunction, systemic sepsis, composite morbidity, and postoperative length of stay, compared to matched patient who did not receive blood.<sup>110</sup>

The American Society of Anesthesiologists (ASA) guidelines recommend RBC transfusion if the Hb concentration drops <6–10 g/dL. While transfusions in patients with a Hb >10 g/dL are rarely indicated, there is little debate that patients with a Hb <6 g/dL should be transfused according to most clinical practice guidelines.<sup>111</sup> A restrictive strategy for young healthy trauma patients where allogeneic transfusion is not performed in asymptomatic patients at rest unless Hb drops <5 g/dL was reported to be safe and have a lower complication rate than a more liberal transfusion strategy.<sup>112</sup> Recent clinical trials have provided Level 1 evidence to support restrictive RBC transfusion practices.<sup>113</sup> Lower transfusion triggers have been shown to be safe<sup>114</sup> and effective for patients undergoing cardiac surgery<sup>115</sup> and critically ill patients.<sup>116</sup> The FOCUS trial found that elderly (mean age older than 80 years), high-risk (factors for coronary artery disease) patients who have undergone hip fracture surgery tolerate a Hb trigger as low as 8 g/dL (or higher if symptomatic).<sup>117</sup> A Cochrane meta-analysis of prospective randomized trials comparing Hb thresholds of >3,700 patients found that low Hb thresholds were well tolerated, and reduced blood transfusions by 37% and perioperative infections by 34%. The meta-analysis concluded that a Hb cut-off level of 7 g/dL was appropriate for most patients.<sup>118</sup> Additionally, a randomized controlled trial of 2,016 elderly patients with history or risk factors of cardiovascular disease who underwent hip surgery demonstrated that mortality rates, inability to walk independently, and in-hospital morbidity rates were similar in liberal versus restrictive transfusion protocols, despite significant fewer transfusions in the restrictive group.

Setting a transfusion trigger is ultimately the function of the underlying health of the patient, the change in the level of Hb, the absolute level of Hb, and any decrease in perfusion. Monitoring for perfusion of vital organs using standard ASA recommendations includes heart rate, blood pressure, oxygen saturation, capnography, and urine output in addition to clinical evaluation.<sup>119</sup> The American College of Physicians does not identify a discrete Hb level as a trigger for transfusion. Instead, it recommends basing the decision

on clinical evaluation, and if needed, transfusing only one unit and reevaluating the situation.

## Conclusion

The changing landscape of health care demands improved quality of care while reducing costs, and highlights the importance of efficient and cost-effective blood management in elective procedures. Future directions in blood management ultimately must rely on defining anemia treatment thresholds in specific patient populations, and a deeper understanding of how patients may be able to tolerate different levels of Hb reduction based on their individual background, level of conditioning, and associated comorbidities. Evidence of benefit from RBC transfusion is hard to find, and most benefit from RBC transfusion is assumed and not scientifically proven.

A multimodal strategy for reducing blood loss should be adopted as the standard of care in surgical patients at risk of blood transfusion. The plan of care should be tailored to the individual patient's condition and to the type of procedure to be performed. Individual preoperative assessment of transfusion risk is crucial to identify the best-suited modalities to minimize blood requirements. The use of antifibrinolytic drugs, namely TXA, should be considered in major surgery. The use of intraoperative or postoperative cell salvage (washed or filtered) should be limited to procedures in which cost effectiveness has been established. Bloodless procedures can only be achieved through patient-tailored protocols that employ the best-suited modalities for each individual patient, maximizing efficacy while reducing cost and adverse effects.

## Disclosure

The authors report no conflicts of interest in this work.

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