



Post-operative Anemia After Major Surgery: a Brief Review

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Abstract

Purpose of Review Anemia is a very common complication in the post-operative period. Post-operative anemia is associated with poor outcomes including but not limited to infections, increased length of stay, circulatory overload, and mortality. The strategy of patient blood management focuses on three pillars that include the detection and treatment of pre-operative anemia; reduction of peri-operative blood loss; and harnessing and optimizing the patient-specific physiological reserve of anemia.

Recent Findings Multiple studies in surgical patients have been conducted to study various methods of management of post-operative anemia. Recent advances in surgical techniques have also been studied to minimize blood loss. There is a widespread consensus on the use of intravenous iron in hospitalized post-operative patients after major surgery.

Summary We discuss the most common causes of post-operative anemia and management focusing on measures to reduce blood loss and measures to increase red blood cell (RBC) mass. In this brief review, we present updates from the most relevant articles in the past 5 years and include updates from the 2018 international consensus statement on the management of post-operative anemia after major surgical procedures.

Keywords Anemia · Post-operative anemia · Peri-operative anemia · Intravenous iron · Post-operative evaluation · Peri-operative care

Introduction

Anemia is a very common complication in the post-operative period after a major surgery. The World Health Organization (WHO) defines anemia as a hemoglobin (Hgb) of <13 g/dL for men and <12 g/dL for women. Post-operative anemia is associated with poor outcomes including but not limited to infections, increased length of stay, circulatory overload, and mortality. Prevalence of post-operative anemia can be in the

range of 80–90% after major surgery [1]. Understanding the cause of the anemia is the key to management of post-operative anemia. The concept of patient blood management (PBM) was introduced in 2005 and is being utilized in healthcare institutions worldwide. This strategy focuses on three pillars: the detection and treatment of pre-operative anemia; reduction of peri-operative blood loss; and harnessing and optimizing the patient-specific physiological reserve of anemia (including restrictive hemoglobin transfusion triggers) [2]. In this brief review, we discuss the most common causes of post-operative anemia and present updates from the most relevant articles in the management of post-operative anemia in the past 5 years.

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Causes of Post-operative Anemia

Post-operative anemia after major non-cardiac surgeries may be due to worsening of pre-operative anemia, peri-operative blood loss (intra-operative blood loss, coagulopathy, and phlebotomy), and post-operative reduced erythropoiesis due to surgery-associated inflammation. Inflammatory cytokines after surgery can lead to a cascade of effects where increased hepcidin degrades the iron exporter ferroportin causing iron

sequestration in macrophages. Active inflammation also leads to decreased iron uptake from the gastrointestinal tract and a diminished erythroid response to erythropoietin. This results in delayed recovery of hemoglobin post-operatively. Patients with cancer are at specially increased risk of bleeding due to multiple factors which include activation of procoagulant and antifibrinolytic pathways, effects of chemotherapy leading to anemia, thrombocytopenia and endothelial dysfunction, and, in some cases, close proximity or invasion into vasculature as well as hypervascularization of tumor itself [3]. Other factors are hemodilution from excessive peri-operative fluids (which may exacerbate pre-existing anemias), nutritional deficiencies, and pharmacological interactions. Low pre-operative hemoglobin, female sex, and smaller body surface area have been identified as risk factors for the development of post-operative anemia and increased transfusion needs [4]. An estimation of surgical blood loss after common surgeries is summarized in Table 1 [5].

Ongoing post-operative blood loss can continue through drains or into traumatized tissue, or due to repeated phlebotomy during prolonged post-operative hospitalization. As such, peri-operative blood loss may result in acute or late post-operative anemia. In general, hospitalists may consider the more common and major causes of anemia in surgical patients: iron deficiency anemia, anemia of chronic disease, and macrocytic anemia (of which vitamin B12 and folate deficiencies account for more than 95% of cases).

Management of Post-operative Anemia

The management of post-operative anemia should focus on correction and optimization of pre-operative anemia and hematinic deficiencies as well as preventing intra-operative blood loss. Ideally, this process should be started several weeks pre-operatively.

Measures to Reduce Blood Loss There are several medical, surgical, and anesthesia measures that can reduce the occurrence of post-operative anemia. Careful medication management helps minimize bleeding peri-operatively. This includes appropriate hold times for antiplatelets and anticoagulants. Medications like antiinflammatory agents, selective serotonin reuptake inhibitors, ginkgo, ginseng, and garlic interfere with hemostasis and should be held prior to surgery. Drugs such as amiodarone, fluconazole, rifampin, and phenytoin interact with direct oral anticoagulants (DOAC's) and can increase bleeding risk. The use of inappropriate bridging anticoagulation has been associated with increased peri-operative bleeding [6]. Restarting antiplatelet and anticoagulant medications prior to achieving hemostasis also increases peri-operative blood loss. The American College of Cardiology (ACC) consensus guidelines for peri-operative anticoagulation management in non-valvular atrial fibrillation recommend careful

consideration of bleeding consequences, especially with high-risk bleeding procedures such as open cardiac, intracranial, and/or spinal procedures [7]. The ACC guidelines also include consideration of patient-specific factors that may predispose to bleeding complications (like bleeding diathesis, platelet dysfunction, antiplatelet medication). Following procedures with a low risk of post-procedural bleeding, therapeutic anticoagulation can generally be started within 24 h of surgery in collaboration with a proceduralist. However, following procedures with high bleeding risk, therapeutic parenteral anticoagulation or DOAC use should be delayed for at least 48–72 h after the procedure [7]. Table 2 summarizes the bleeding risk associated with commonly performed procedures [8, 9]. Foregoing daily phlebotomy in stable patients decreases iatrogenic anemia and is not associated with increased readmissions or mortality. Every 100 mL of phlebotomy is associated with a hematocrit decrease of 1.9% [10].

Combined with modern blood management protocols, acute normovolemic hemodilution (ANH) and cell salvage are only beneficial in high bleeding risk (> 1000 mL) surgeries. ANH is the donation of whole blood immediately prior to surgery with the use of colloid or crystalloid fluids to maintain a hematocrit of around 20–30% [11]. Subsequently, less blood is lost during surgery, and donated blood is returned to the patient at wound closure. Cell salvage involves the collection of shed blood during surgery and the return of washed or filtered blood to the patient [2]. Although cell salvage is cost-effective compared to blood transfusion, its efficacy can be reduced by simultaneous use of antifibrinolytic and hemostatic agents. Potential harms from cell salvage include re-introduction of bacteria and malignant cells from contaminated field.

Another routinely used intra-operative technique is surgical drains. Drains can decrease compression of vital structures and reduce hematomas. However, the use of drains is controversial due to concern for increased bleeding. When they are used, clamping of drains 4 to 6 h post-operatively may reduce blood loss [12].

Antifibrinolytic agents like the synthetic lysine analog tranexamic acid (TXA) reduce blood loss by inhibiting activation of plasminogen to plasmin and preventing the degradation of fibrin. It is safe and effective in intravenous and topical forms with no increase in thromboembolism rates [12, 13]. It has been shown to be efficacious and recommended for use with high bleeding risk surgeries like hip and knee replacements [14] as well as cardiac surgeries [15].

Neuraxial anesthesia can decrease bleeding by 20–30% through systemic hypotension and decrease in venous tone due to sympathetic blockade [2, 11]. Hypothermia, acidosis, and hypocalcemia inhibit hemostasis due to impaired platelet function and enzymatic clotting factors and thus should be avoided. Patient positioning to reduce obstruction of venous return also decreases local bleeding [2, 11].

Table 1 Estimated blood loss with common major surgeries [5]

Common surgical procedures	Estimated blood loss	
Orthopedic surgeries	Shoulder arthroplasty	200–1000 mL
	Total knee arthroplasty: primary; revision	300–500 mL; 500–1000 mL
	Total hip arthroplasty: primary; revision	250–750 mL; >1000 mL
	Acetabular fracture open repair	100–2000 mL
Neurosurgical surgeries	Hip fracture repair	100–500 mL
	Cervical/lumbar laminectomy	25–500 mL
	Cervical corpectomy and fusion	50–1000 mL
	Transthoracic spine surgery	200–5000 mL (non-tumor cases: 200–400 mL)
	Lumbar fusion and fixation	250–1000 mL
Cardiothoracic surgeries	Microdiscectomy	25–100 mL
	Craniotomy	50–500 mL (meningioma and renal cell are highly vascular)
	Coronary artery bypass	500–600 mL
	Surgical valve replacement (aortic and mitral)	300–400 mL
	Heart transplant	500–1500 mL
	Lobectomy, pneumonectomy, wedge resection	<500 mL
	Heart-lung transplant	500–2000 mL
	Lung transplant: single; double	500 mL; 500–2000 mL
Vascular surgery	Carotid endarterectomy	100–200 mL
	Aortic aneurysm repair: thoracic; abdominal (open)	300–400 mL; 500 mL
	Acute aortic dissection	400–800 mL
	Infrainguinal arterial bypass	200–300 mL
General surgery	Esophagectomy	300–800 mL
	Sleeve gastrectomy or Roux en Y	<500 mL
	Gastrectomy: partial; total	100–500 mL; >500 mL
	Whipple's procedure	500–750 mL
	Appendectomy	<75 mL
	Cholecystectomy	Minimal–250 mL
	Renal transplant	100–200 mL
	Liver transplant	1500 mL average (may require up to 100 units due to associated coagulopathy)
Obstetrics & gynecological	Hysterectomy: abdominal; vaginal	200–300 mL; 100–200 mL
	Radical hysterectomy	500–1500 mL
	Cesarean section: lower segment; classic	750–1000 mL; 1000–2000 mL
Urological	Transurethral resection or prostate (TURP)	500 mL
	Nephrectomy: simple; partial	500 mL; 1200 mL
	Cystectomy	Minimal–1500 mL depending on extent
Otolaryngology	Laryngectomy	50–300 mL
	Neck dissection	200–400 mL
	Thyroidectomy	50–75 mL

Measures to Increase RBC Mass or Hemoglobin Blood transfusion still remains the default treatment for post-operative anemia and works rapidly. There are obvious benefits of quickly increasing the hemoglobin concentration in patients with chest pain, hemodynamic instability, or hypotension unresponsive to fluids. However, for the majority of patients, rapid correction is not indicated and, in fact, may be detrimental. The hazards of

transfusion include immunomodulatory effects, risks of circulatory overload, transfusion reactions, and infective complications. The immunomodulatory effects of transfused blood include increased cancer recurrence, metastasis, and post-operative infection [2]. It has been well established that the restrictive strategy of targeting hemoglobin of 7 g/dL is as effective and may be superior to the liberal strategy of targeting

Table 2 Bleeding risk associated with common procedures [8, 9]

	High bleeding risk	Low bleeding risk
Neurological	Intracranial or spinal surgery	
Cardiac	Cardiac surgery (bypass, valve replacement)	Pacemaker and defibrillator implant placement, coronary angiography
Vascular	Major vascular surgery (aortic aneurysm, vascular bypass)	Peripheral vascular stent placement
Thoracic	Lung resection	
Abdominal/pelvic	Major abdomino-pelvic surgeries (pancreatic resection, bowel resection, hepatobiliary, endometrial/ovarian cancer resection)	Cholecystectomy, hernia repair, hydrocele repair, colonoscopy with biopsy, hysteroscopy
Orthopedic	Major orthopedic surgeries (hip fracture, hip, knee and shoulder arthroplasty)	Hand and foot surgery, arthroscopic surgery
Otolaryngological	Major surgery of head and neck (cancer resection, reconstruction)	Fiber optic laryngoscopy
Urological	Urologic surgery (radical prostatectomy, bladder resection)	Cystoscopy, hydrocelectomy
Common biopsies	Kidney, liver, polypectomy	Dermatologic, thyroid, breast, lymph node
Anesthesia techniques	Neuraxial (spinal, epidural)	General
Ophthalmologic	Orbital decompression, retinal surgeries	Cataract

hemoglobin of 10 g/dL in critically ill patients [16]. This has also been studied in elderly patients with high cardiovascular risk where liberal transfusion did not reduce the rate of death or in-hospital morbidity compared with restrictive strategy [17]. The American Association of Blood Banks (AABB) in their guidelines in 2016 recommended adopting a policy for restrictive transfusion (7 to 8 g/dL) in stable hospitalized patients. These guidelines recommended a threshold of <7 g/dL in all surgeries except in cardiac surgery and orthopedic surgery patients where a threshold of ~8 g/dL was recommended [18]. More recently, an international conference on PBM released a consensus statement recommending a restrictive transfusion threshold as well. Some of these recommendations are summarized in Table 3 [19].

Iron deficiency remains common in post-operative period and should be corrected. However, in the post-operative period, oral iron is often not tolerated or absorbed. Hepcidin synthesis and release during surgery is increased which in turn inhibits intestinal iron absorption, making oral iron therapy largely ineffective. Intravenous (IV) iron is, therefore, preferred for correction. Both pre-operative and post-operative administration of IV iron with or without erythropoietin-stimulating agents (ESA) has been found to be a safe and effective way for correcting anemia after a variety of major surgeries [20, 21]. In patients undergoing major abdominal surgery, pre-operative intravenous iron was associated with a 60% reduction in the need for allogenic blood transfusion [21]. It was also associated with a shorter hospital stay, enhanced iron stores, and higher mean Hgb concentration 4 weeks after surgery [21]. An international consensus statement on the management of post-operative anemia recommends that, where possible, it should be administered using a single high dose preparation for the repletion of iron stores

[4]. Currently, six intravenous iron formulations are available in the USA [4, 22] (Table 4). Intravenous direct iron preparations have existed since 1940s but were feared as a large release of elemental iron caused severe adverse events (SAE) including anaphylaxis. In 1964, high molecular weight iron dextran which had a slower release of elemental iron gained popularity but still had a 1–2% risk of SAE. In 1991, a different preparation, low molecular weight iron dextran was approved for widespread use as studies showed the dextran moieties of low molecular weight iron dextran were less immunogenic. However, it still carried a black box warning for anaphylaxis and currently requires a test dose. Many clinicians and health authorities still consider that IV iron is strongly associated with major side effects such as anaphylaxis, infection, or oxidative stress. However, these side effects appear not to be significant with the newer IV iron preparations [4]. One study in 2002 [23] concluded that compared to iron dextran, iron sucrose and iron gluconate are far less immunogenic because of their carbohydrate moiety. However, they release less elemental iron per dose and require multiple dosing. Ferumoxytol, another newer formulation caused significant hypotension when infused rapidly and hence carries a black box warning that recommends prolonged infusions over 15 min. Ferric carboxymaltose is better tolerated and more effective than other intravenous iron preparations especially in treating inflammatory bowel disease-related anemia [24]. Recently approved ferric derisomaltose can be given as a single infusion with a similar safety profile as iron sucrose [25].

The choice of which formulation to use often depends on the institutional availability. It has long been suggested that patients with iron overload are at increased risk of infection. Data from meta-analyses and large observational studies showed that peri-operative IV iron did not increase post-

Table 3 Recommendations for transfusion threshold [19]

Type of surgery	Recommendation; Hgb threshold
Non-cardiac surgery (excluding hip fracture) in a hemodynamically stable patient	Restrictive; < 7 g/dL
Cardiac surgery	Restrictive; <7.5 g/dL
Hip fracture in patient with underlying cardiovascular disease or other risk factors	Restrictive; <8 g/dL
Critically ill but hemodynamically stable patient	Restrictive; 7 g/dL
Acute gastrointestinal bleeding in a hemodynamically stable patient	Restrictive; 7–8 g/dL

operative infection or 30-day mortality rates in surgical patients. However, in the absence of definitive clinical data, it would seem logical to refrain from IV iron administration in the setting of acute infection [4].

Prevalence of vitamin B12 and folate deficiency in patients with anemia is low in peri-operative period. Nonetheless, when such deficiencies are noted, they should be corrected promptly. Patients undergoing gastric bypass surgery especially Roux-en-Y should have pre-operative assessment of vitamin B12 levels and any deficiency should be treated. Iron deficiency remains prevalent in this population and one study found that the rate of iron deficiency increased from 6% pre-operatively to 42% post-operatively in female patients [26]. This further reinforces the need to correct all nutritional deficiencies prior to elective surgery.

Erythropoietin-stimulating agents (ESA) are increasingly being used both in pre- and post-operative settings for correction of anemia along with iron supplementation. In addition to stimulating erythropoiesis in post-operative period, a single dose of ESA can also decrease serum levels of hepcidin. A Cochrane review of recombinant erythropoietin (rEPO) in patients with colorectal cancer failed to show any significant change in hemoglobin level with pre-operative use of rEPO, or a decrease in the number of patients receiving allogeneic blood transfusion [27]. However, a study of combined therapy

of IV iron and recombinant human erythropoietin in anemic patients undergoing cardiac valve replacement surgery was associated with decreased length of stay, decreased blood transfusion, and improved survival [28]. Previously, a systematic review of erythropoietin use in patients undergoing orthopedic and cardiac surgery showed a reduction in the proportion of patients receiving allogeneic blood transfusions [29]. Potentially harmful effects include hypertension, and thrombotic and ischemic events.

For non-cancer patients with severe post-operative anemia and inflammation-induced blunted erythropoiesis, or those declining blood transfusion (for e.g., Jehovah’s witness), consideration should be given to additional treatment with an ESA [4]. In fact, for a special population like Jehovah’s witness, their beliefs mainly preclude blood transfusions and they are often willing to accept both IV iron and ESA. In a recent thought-provoking study in patients undergoing cardiac surgery, the authors used an ultra-short-term treatment of patients with intravenous iron, ESA, vitamin B12, and folic acid a day before surgery. This strategy was associated with a decrease in the need for RBC transfusion within 7 days and up to 90 days after surgery [30]. This may be a useful strategy for urgent and time-sensitive surgeries where optimization of pre-operative anemia is often not possible. It may also be a consideration in a patient’s declining blood transfusion like Jehovah’s witness.

Table 4 Different formulations of IV iron available in the USA [4, 16]

Generic name	Iron dextran	Sodium ferric gluconate	Iron sucrose	Ferumoxytol	Ferric carboxymaltose	Ferric derisomaltose (iron isomaltoside)
US brand name	Infed	Ferrilict	Venofer	FerraHeme	Injectafer	Monoferric
Approval date	1991	1999	2000	2009	2013	2020
Plasma half-life (h)	20	1	6	15	16	20
Needs test dose	Yes	No	No	No	No	No
Black box warning	Yes	No	No	Yes	No	No
Single total dose infusion	Yes	No	No	No	No	Yes
Suggested dosage and frequency (for 1000 mg deficit)	25mg test dose then 1000 mg single dose	125 mg IV up to 8 doses	200 mg up to 5 doses	510 mg every 3–8 days for total 2 doses	15mg/kg every 7 days for 2 doses	1000 mg single dose

Conclusion

Although the cause of post-operative anemia is multifactorial, it is often considered to be reflective of peri-operative blood loss. A targeted approach to correcting pre-operative anemia, minimizing peri-operative blood loss and establishing restrictive transfusion threshold and use of intravenous iron therapy are key components of management of post-operative anemia.

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