Perioperative anaemia management

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Abstract: Roughly a third of surgical patients are found to have preoperative anaemia, with increased prevalence seen in children and the elderly, females, and residents of low-income regions. Perioperative anaemia is independently associated with poorer outcomes in surgery, which warrants a proactive approach to evaluation and management of anaemia. As allogeneic red blood cell (RBC) transfusion is associated with increased risk of infection and many comorbidities in patients, other modalities for treatment of anaemia and mitigation of blood loss should be employed. The appropriate approach to treatment of preoperative anaemia will depend on investigation of the patient's underlying pathophysiology. The most common cause of preoperative anaemia is iron deficiency. Oral iron supplementation or intravenous (IV) iron, sometimes combined with erythropoiesis stimulating agents (ESAs), can effectively correct iron-deficiency anaemia prior to surgery. Techniques of intraoperative blood conservation, including intraoperative cell salvage and acute normovolemic hemodilution (ANH), along with hemostatic agents can reduce surgical blood loss and limit the need for allogeneic RBC transfusion. Effective care of the postoperative patient requires attention to limiting blood draws, optimizing nutrition, and judicious utilization of pharmacologic agents and blood component therapy. Increasing awareness of patient blood management as an overall approach and growing evidence of improved patient outcomes with blood conservation strategies will likely lead to increased adoption of best practices for management of perioperative anaemia.

Keywords: Anaemia; perioperative anaemia; surgery; patient blood management (PBM)

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Introduction

Anaemia is common finding in patients who are planned for surgical intervention or undergoing emergency surgery and the incidence may be as high as a third of patients pre-surgery (1). Perioperative anaemia is associated with poorer outcomes in surgery even if it is mild in severity (2,3). Anaemia acts synergistically with other comorbidities, i.e., heart and renal failure, in what is known as cardiorenal anaemia syndrome (4) further worsening patients' outcomes.

Nonetheless, anaemia is not just an 'innocent bystander', and if left unmanaged, it can severely affect patient outcomes, quality of life and impose a significant burden on the healthcare system (5). The National Institute for Health and Care Excellence [2015] guidelines (6) therefore state that all non-urgent surgery should be delayed to allow optimization of anaemia. One of the strategies to manage such perioperative anaemia may be blood transfusion and restoration of hemoglobin level. But transfusion has multiple associated complications including alloimmunization, transfusion-transmitted diseases, transfusion reactions, etc. Blood is also a limited and costly resource. So, in the last few decades the focus has shifted from blood transfusion and transfusion threshold concept to the importance of diagnosing, treating and preventing, the underlying causes of anaemia. In the recent concept of health care landscape, patient blood management (PBM) in surgical cases has been aimed at individual patient centered anaemia management to optimize patient outcomes. Adequate treatment of anaemia reduces the need for transfusion along with its associated risks and reduces the length of stay, consequently lessening health-care expenditure (7).

Epidemiology—prevalence of perioperative anaemia

Preoperative patients present with anaemia at a rate higher than the general population. The prevalence of preoperative anaemia varies according to the medical or surgical condition being treated and demographic variables such as age, gender, and geographical region. Observational study results for preoperative anaemia prevalence differ based on study exclusion and inclusion criteria such as exclusion of specific patient types (e.g., obstetric, pediatric, transplant) and inclusion of emergency or minor surgeries. Additionally, the definition of anaemia utilized affects the study's estimate of prevalence. The majority of studies in the literature use the World Health Organization (WHO) definition of anaemia: hemoglobin less than 130 g/L for men and less than 120 g/L for women. However, some studies use a criterion of hemoglobin less than 130 g/L for both males and females. Since females generally have a smaller body surface area and lower total blood volume compared to males, an equivalent loss of blood volume during surgery represents a higher proportion of hemoglobin mass lost and a concomitantly higher likelihood of red blood cell (RBC) transfusion. Therefore, utilizing a criterion of hemoglobin less than 130 g/L for preoperative anaemia in females may be more appropriate.

Results from the International Surgical Outcomes Study (ISOS) showed 30.1% of adult elective inpatient surgery patients in 27 countries had preoperative anaemia (8). This result is comparable to the preoperative anaemia prevalence of 27.6% found in a large retrospective study of Chinese adult patients (9), 28.7% reported in a large prospective European cohort study of adult non-cardiac, non-obstetric, non-neurological surgery patients (10), and 47.8% seen in a large prospective observational study of adult non-cardiac, non-obstetric surgery patients across South Africa (11). Anaemia prevalence is increased in the elderly, in females, and in less wealthy regions (9,12).

Preoperative anaemia prevalence differs significantly based on type of surgery. Patients undergoing elective total joint arthroplasty for knee or hip showed preoperative anaemia prevalence of 19.6% in a retrospective review of 15,722 patients (13). Preoperative anaemia is much more common in surgery after hip fracture, with prevalence of 65% shown in retrospective review of 34,805 patients in the National Surgical Quality Improvement Program (NSQIP) database (14). The prevalence of preoperative anaemia in patients undergoing colectomy for colon cancer is significant, and was found to be 50.4% in a retrospective review of 35,243 patients in the NSQIP database (15). For the adult cardiac surgery patient population, preoperative anaemia prevalence from 15% to 54% has been reported (16,17), with most studies reporting a prevalence between 25% to 40% (18,19).

Pathophysiology of perioperative anaemia

While preoperative anaemia may result from any of a number of pathologies, the majority fall under acute hemorrhage, chronic blood loss, chronic inflammation, chemotherapy and radiotherapy, and nutritional deficiencies, the most common of which is iron deficiency.

Acute hemorrhage and chronic blood loss

Preoperative anaemia can result from acute hemorrhage in specific emergency surgery settings, e.g., ruptured abdominal aortic aneurysm, traumatic injury. Chronic blood loss may occur with gastrointestinal disorders such as ulcers, polyps, or colorectal cancer; tumors of the kidney or bladder; and heavy menstrual bleeding.

Chronic inflammation

Anaemia of chronic inflammation occurs with systemic inflammation and activation of immune mediators seen in a multitude of disease groups including chronic kidney disease, malignancy, autoimmune diseases, and congestive heart failure, among others (20). Activated immune mediators impede erythropoiesis by inhibiting synthesis of erythropoietin

(EPO) by the kidneys and decrease the stimulatory effect of EPO on erythroid progenitor cells (17,21). Upregulation of cytokines induces hepcidin, inhibiting absorption of dietary iron and promoting iron retention in the storage pool (reticuloendothelial cells) (12,20).

Chemotherapy and radiotherapy

Myelosuppressive chemotherapeutic drugs cause anaemia through direct impairment of hematopoiesis in the bone marrow (22). Cytotoxic drugs with nephrotoxic side effects (e.g., platinum-containing agents) can cause anaemia by decreasing synthesis of EPO by the kidneys (22). Radiation therapy damages the bone marrow, reducing production of erythrocytes (23).

Absolute iron deficiency

Absolute iron deficiency describes depletion of total-body iron stores due to (I) inadequate iron intake relative to physiologic requirements, (II) defective absorption, or (III) chronic blood loss. In developing countries, iron deficiency anaemia may result from blood loss associated with certain parasitic infections, such as malaria, schistosomiasis, or hookworm infection (24,25). Reduced absorption may occur due to atrophic gastritis or upregulated levels of hepcidin in chronic inflammatory states (24).

Functional iron deficiency

While the storage pool of iron resides in the liver, spleen and lymph nodes, the functional pool of iron is found within RBCs, bone marrow and cardiac and skeletal muscle (26). Functional iron deficiency results from chronic inflammation and the ensuing cytokine and hepcidin release. Hepcidin not only decreases iron absorption in the duodenum but also causes iron retention within the storage pools through blockage of ferroportin (26). Thus, even in the presence of normal levels of storage iron, functional iron deficiency can lead to anaemia.

Other nutritional deficiencies—vitamin B12 and folic acid

Nutritional deficiencies of vitamin B12 (cobalamin) or folic acid, both essential for erythropoiesis, lead to anaemia. Vitamin B12 deficiency occurs due to poor nutrition or impaired absorption. Intrinsic factor, produced in the stomach and required for absorption of vitamin B12 in the distal ileum of the small intestine, may be deficient due to autoimmune pathology or gastric achlorhydria associated with *Helicobacter pylori* infection or gastric resection/bypass surgeries (21,27). Nutritional deficiency of folic acid results from inadequate intake or malabsorption due to intestinal diseases, previous surgical resection or bypass of intestine, excessive alcohol consumption, or some medicines (e.g., phenytoin, carbamazepine, gabapentin) (21,28).

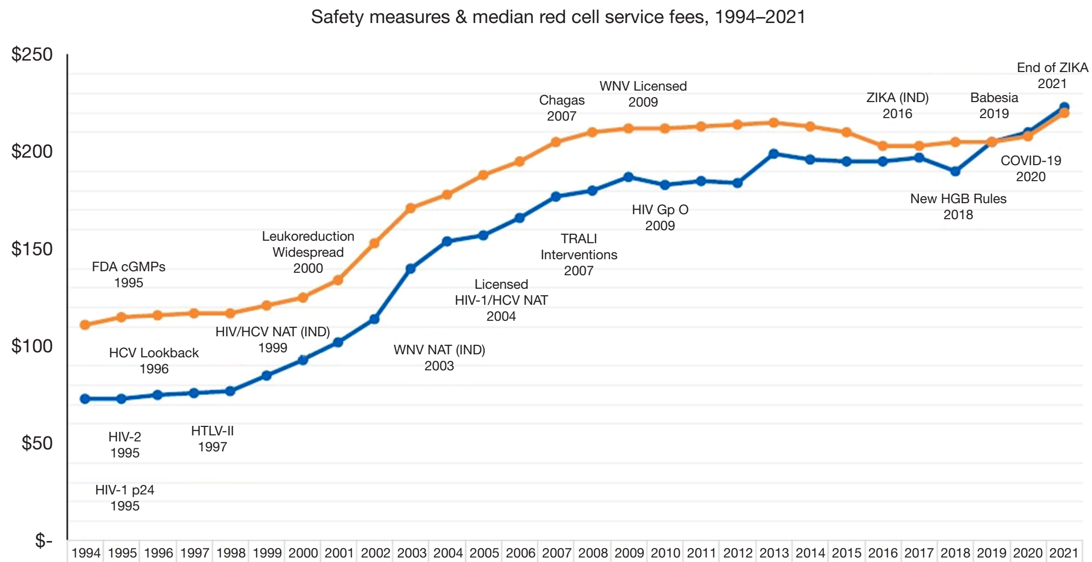
Causes of intraoperative and postoperative anaemia

Intraoperative and postoperative anaemia may result from acute normovolemic hemodilution (ANH) techniques for blood conservation or from infusion of priming solutions through the cardiopulmonary bypass circuit prior to cardiac surgery. Blood loss during and after surgery are also major causes of intraoperative and postoperative anaemia.

Outcomes of perioperative anaemia

The association of anaemia with perioperative morbidity and mortality is well described in the literature. Risk for perioperative morbidity and mortality is also correlated with patient American Society of Anaesthesiology (ASA) score, and perioperative anaemia is associated with allogeneic RBC transfusion, an independent risk factor for infection and other morbidities. Allogeneic RBC transfusion and patient preoperative ASA score are confounding factors in most studies of the effect of perioperative anaemia on morbidity and mortality. Some but not all studies have adjusted for these confounding factors in analysis to establish perioperative anaemia as an independent risk factor for morbidity and mortality.

Secondary analysis of the ISOS data from 38,770 patients showed increased risk of in-hospital death within 30 days of surgery for patients with moderate and severe preoperative anaemia compared to patients without anaemia. All grades of preoperative anaemia were associated with an increased risk of experiencing a complication (e.g., infection, cardiovascular complication, or other complication) (8). Analysis of data from NSQIP database for 227,425 patients undergoing non-cardiac surgery showed higher postoperative mortality and higher incidence of one or more major postoperative morbidities in patients with any grade of preoperative anaemia compared to non-anaemic patients (3). Postoperative complications and mortality after cardiac surgery and their association with preoperative and intraoperative anaemia have been widely studied. A



	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
RBCs	$73	$73	$75	$76	$77	$85	$93	$102	$114	$140	$154	$157	$166	$177	$180	$187	$183	$185	$184	$199	$196	$195	$195	$197	$190	$205	$210	$223
RBCs, LR	$111	$115	$116	$117	$117	$121	$125	$134	$153	$171	$178	$188	$195	$205	$210	$212	$212	$213	$214	$215	$213	$210	$203	$203	$205	$205	$208	$220

Figure 1 Investment in safety advancements *vs.* declining price of blood to pay for those safety mandates (34). cGMPs, cyclic guanosine monophosphates; COVID-19, coronavirus disease 2019; FDA, Food and Drug Administration; HIV Gp O, HIV group O; HCV, hepatitis C virus; HGB, haemoglobin; HIV, human immunodeficiency virus; HTLV-II, human T-lymphotropic virus type II; IND, individual; NAT, nucleic acid amplification test; LR, leukoreduced; RBCs, red blood cells; TRALI, transfusion related acute lung injury; WNV, west nile virus; ZIKA, Zika virus.

multicenter cohort study of cardiac surgery patients at seven academic hospitals in Canada showed patients with preoperative anaemia had an increased incidence of in-hospital outcomes (e.g., composite of death, stroke, or acute kidney injury) after adjusting for confounding variables including intraoperative RBC transfusion (18). A single-center study of 7,957 cardiac surgery patients who did not receive RBC transfusion intraoperatively evaluated the nadir hematocrit during cardiopulmonary bypass and its association with end-organ dysfunction and mortality. A lower intraoperative nadir hematocrit was associated with worse renal function as measured by estimated glomerular filtration rate, more myocardial injury indicated by higher troponin level, longer postoperative ventilator support, longer hospital stays, and higher mortality (29).

Transfusion *vs.* management of anaemia

The use of allogeneic blood transfusion to manage anaemia and blood loss is a concept that originated several centuries ago and has changed little over the years. Blood collection has historically lagged demand, resulting in a blood supply that is insufficient to meet transfusion needs. Challenges in supply chain may be related to local causes, this includes a high prevalence of infectious disease, the coronavirus disease (COVID) pandemic or sudden epidemics (30-32).

Though the safety of the blood supply has improved markedly with sophisticated testing and public demand for a "zero-risk blood supply" has led to a dramatic decline in the risk of transfusion-transmitted human immunodeficiency virus (HIV), hepatitis C virus, and hepatitis B virus, there is concurrent increase in transfusion related emerging infectious diseases such as West Nile, Zika, and chikungunya viruses (33). Sometimes when newly emergent infections arise, the potential for spread by transfusion is unknown. There is also risk of transfusion related adverse incidents such as transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), hemolytic transfusion reactions, allergic reactions, alloimmunization and immunomodulation, etc. In some instances, these may be life-threatening. The cost of processing of blood units may be another important factor to consider using blood judiciously as additional testing and regulatory measures have contributed to increases (34) (*Figure 1*). America's Blood Centers Financial Ratio Survey, 2022 has shown the financial impact of blood transfusion while ensuring its safety.

On the other hand, prevention, while the diagnosis and management if anaemia in perioperative scenario may be time consuming, it has several advantages. In a scenario of a patient with rare blood group and alloimmunization with multiple antibodies against high prevalence antigens or where the patient does not consent for blood transfusion as with the case of Jehovah's Witness patients, perioperative anaemia management may be the only feasible option.

Preoperative anaemia management

Screening, evaluation, role of pharmacologic agents

A European surgical outcome study of patients undergoing non-cardiac and non-neurological surgery revealed preoperative anaemia to be an independent risk factor for higher in-hospital mortality, longer hospital length of stay, and postoperative intensive care admission (10). Other studies have also found an increased risk of perioperative blood transfusion (35,36). Transfusion, independent of preoperative anaemia, has a dose-dependent increase in complications and mortality of up to 10 folds in patients with lowest predicted risk (37). This underpins the importance of screening targeted elective surgical patients for preoperative anaemia. The screening should be carried out commonly 4 to 8 weeks before the scheduled surgical procedure to allow for sufficient time for investigation, and correction of anaemia (37).

If hemoglobin screening detects anaemia, evaluation should start with a detailed clinical history because anaemia is a symptom of an underlying disease. This evaluation should include nutrition history, history of bleeding especially gastrointestinal hemorrhage. Clinical history is also important to guide the choice of investigation. Of all the causes of anaemia, iron deficiency is the commonest worldwide (38).

Laboratory investigations to evaluate preoperative anaemia should be tailored towards the most common causes based on epidemiological findings. In low-income countries, anaemia due to nutritional deficiencies, and infections/infestations are the most prevalent. Other causes of anaemia include malignancies and chronic renal failure. Therefore, the following laboratory investigations are pertinent for anaemia evaluation: hemoglobin and/or hematocrit, serum ferritin, transferrin saturation, serum vitamin B12, and renal function tests, as well as C-reactive protein (37).

Considering the burden of iron deficiency, any patient irrespective of gender with hemoglobin of less than 130 g/L should be evaluated for iron deficiency. Serum ferritin is the most predictive test for iron deficiency anaemia; and a value of <30 µg/L is suggestive of absolute iron deficiency anaemia with a sensitivity and specificity of 92% and 98%, respectively when compared with an empirical iron therapy or a very invasive bone marrow aspiration biopsy study (39). In the setting of inflammation, a patient with serum ferritin 30 to 100 µg/L, transferrin saturation <20%, and/or C-reactive protein >5 mg/L is considered to have low iron stores (40). Suffice to say that if laboratory evaluation rules out absolute iron deficiency or iron mobilization anaemia (due to inflammation or malignancy), measurement of serum creatinine may indicate chronic kidney disease (41).

In megaloblastic anaemia, the mean corpuscular volume (MCV) is often high, sometimes up to 140 fL. It is often due to deficiency of B12 and/or folic acid. The serum B12 is low in megaloblastic anaemia due to B12 deficiency, but serum folate is not a reliable marker for the investigation of folate deficiency as it is often increased in the presence of vitamin B12 deficiency and due to its lability, it is readily corrected by a nutritious meal (42).

Red cell folate is therefore a more accurate guide to tissue folate status (42). Regarding iron deficiency, a therapeutic trial of oral iron therapy could confirm absolute iron deficiency. However, nonresponse to iron therapy could be because of patient non-compliance (43), ongoing blood losses in excess of oral iron absorption (39), or diminished gastrointestinal absorption of iron due to inflammation (44) or local gastrointestinal condition(s). Therefore, treatment strategies that include iron, B12, folate, or even EPO replacement should be considered.

Nutritional deficiencies must be treated with appropriate supplement(s) before an elective surgical procedure. In the case of megaloblastic anaemia, it may be safer to initiate treatment with both B12 and folic acid. Initial treatment with B12 should be started with injection. Iron-deficiency anaemia should be treated with iron supplementation. Iron deficiency anaemia should be treated preoperatively with oral iron as a first-line therapy if there is enough time to produce good outcome before surgery; and this is usually >6 weeks (40). The readily available oral iron formulations are ferrous gluconate, sulfate, and fumarate in 35, 60, and 100 mg of elemental iron per 300-mg tablet, respectively. Studies have shown favorable patients' outcomes when oral iron is given preoperatively, but there appear to be no benefit when given postoperatively (45), probably due to decreased absorption following the inflammatory response to surgery (37).

Intravenous (IV) iron therapy is recommended when oral iron is not tolerated due to gastrointestinal side effects or disorders of gastric or intestinal mucosa that interfere with iron absorption. Timing of the surgery where the planned procedure is less than 4–6 weeks could also be an indication for parenteral iron therapy. If iron and vitamins replacement therapy fail, and hemolysis has been ruled out as a cause of anaemia, then the use of erythropoiesis-stimulating agents (ESAs) such as EPO should be considered (46).

ESA therapy can be effective in treating patients with anaemias of inflammation, chronic kidney disease, or patients with iron deficiency anaemia not responsive to iron therapy alone (46). Suffice to say that patients on ESA should also receive iron therapy to provide adequate iron stores for bone marrow red cell production (46).

Autologous blood donation

Autologous blood transfusion in patients is the safest possible blood as it bypasses the complications associated with allogenic transfusion like alloimmunization, transfusion-transmitted diseases and transfusion reactions. Although autologous blood donation was started more than 150 years ago (47), it gained importance in mid-1980s when the risk of HIV transmission increased (48). Another benefit of autologous blood donation is blood conservation and better patient management. Autologous blood transfusion is life-saving in some patients who do not approve allogenic blood transfusion due to religious beliefs (49). Autologous blood can be collected from 5 weeks to 3 days prior before elective surgery and criteria of blood donation is less stringent than allogenic blood donation. However, the risk of donor bacteraemia and contamination of donated blood unit cannot be totally averted via autologous donation (50). Additionally, the risk of mistransfusion, that is autologous blood getting transfused to wrong patient, cannot be eliminated (51).

A 67% wastage rate in autologous blood has been reported in a study by Perez *et al.* (52). The authors also reported that the preoperative hemoglobin was significantly lower in the autologous donation group compared to control group (133±14 *vs.* 143±15 g/L, P=0.004). Overtransfusion (i.e., use of the unit because it is available) is a common occurrence in autologous blood units which poses significant threat to patient safety and PBM practices.

Intraoperative anaemia management

Intraoperative cell salvage

It is also known as auto-transfusion, blood salvage or cell saver is widely used in orthopaedic (53-55) and cardiovascular (56,57) surgeries. In this method, the shed surgical blood is collected, washed and reinfused in the patient. Autotransfusion using a blood salvage system can have high levels of free hemoglobin or inflammatory mediators (58,59) and might cause coagulopathy (60).

The blood salvage devices used in various operation theatres usually contains four parts (61): one suction line to collect blood from surgical field; a suction system to deliver the blood to collection reservoir which has anticoagulant [heparin (62) or citrate]; a processing bowl which concentrates the red cells and removes plasma or soluble contaminants to waste bag. Finally, the washed blood is emptied into primary reinfusion bag and moved to secondary bag before transfusion (63).

ANH

The ANH technique utilizes removal a controlled volume of whole blood just prior to surgery along with fluid resuscitation so that hemodiluted blood is lost during operation (64). The collected blood is transfused at the end of operation. It is important to define the safe limit of a lower hematocrit of the patient (65), as that is the critical red cell mass (66). The timing of replacement of autologous blood and maintenance of intravascular volume are important key factors for better patient recovery.

In a meta-analysis (67) it has been concluded that ANH in cardiac surgery has significantly reduced transfusion of allogenic blood (P<0.0001). In a multidisciplinary panel (68), it was discussed that ANH cannot be performed in acute infections and hemodynamically significant arrhythmia. A retrospective study on ANH among cancer patients undergoing major surgeries during the COVID-19 pandemic revealed a favorable outcome without any postoperative adverse events (69). The upper and lower limit of blood that can be removed and lower limit of hemoglobin, however, is yet to be studied.

Anaesthesia and role of the surgeon

Hypotensive anaesthesia (70) can be achieved via epidural blockade or IV anesthesia and one advantage is the decrease of post operative blood loss from spill-over hypotensive effect after surgery. Out of all surgeries; head and neck surgeries like functional endoscopic sinus surgery (FESS), free flap reconstruction, head and neck onco-surgery benefit the most from hypotensive anaesthesia (71,72).

One important factor is maintenance of mean arterial pressure close to 60 mmHg since hypotensive anaesthesia is proven to lower the rate of deep vein thrombosis (DVT) and pulmonary embolism (73). By minimizing intraoperative blood loss, disturbances in coagulability decreases. Circulating anticoagulants like anti-thrombin III level decreases intraoperatively due to hemodilution, and there can be post-operative rebound increase in factor VIII which can cause hypercoagulability due to intraoperative blood loss. In this way, hypotensive anaesthesia by decreasing intraoperative blood loss indirectly helps to prevent DVT. Another reason is, if there is excessive fluid resuscitation, hypothermia can occur which triggers Virchow's triad predisposing to DVT (74,75).

The use of a tourniquet in total knee arthroplasty is proven to decrease intraoperative blood loss (76). Bipolar sealers denature collagen of the blood vessel wall to decrease intraoperative blood loss (77). Intramedullary femoral plugs (78) made of acrylic cement or bone grafts significantly reduces mean postoperative drainage.

Computer assisted surgeries are proven to result lower hemoglobin loss in many studies when compared to conventional surgery (79). Patient specific instruments by single use cutting jigs are now widely used in orthopedic surgeries and have considerably reduced allogenic blood transfusion rates (80).

Hemostatic agents (Table 1)

The hemostatic agents (82) such as fibrinogen concentrates, vonicog alfa, susoctocog alfa, idarucizumab, andexanet alfa, and argatroban are widely used in peri-operative bleeding which acts via a procoagulant mechanism. In acute trauma surgeries, antidotes to antithrombotic agents have helped to mitigate bleeding emergencies. Topical hemostatic agents help in reducing operating time and bleeding in gynecology patients (83).

In a study conducted on patients with elective orthopaedic surgery who are hemophiliacs with inhibitors, eptacog alfa has been used in initial bolus dose, which helped in overcoming bleeding episodes perioperatively (84). The off-label use of eptacog alfa has also increased in paediatric cardiac surgery as it acts as effective rescue therapy (85). The hemostatic registry has complied the data regarding off-label use of hemostatic agents in cardiac surgery, traumatic surgery, obstetric surgery and medical bleed over 10 years (86). In UK, tranexamic acid is widely used in cardiac, orthopaedic, liver, gynaecological, neurosurgeries, whereas ε-aminocaproic acid is widely used in USA. Both tranexamic acid and ε-aminocaproic acid are synthetic lysine analogues that act by blocking plasminogen and prevents activation to plasmin, thereby stops fibrin degradation (87).

Post-operative anaemia management

During the post-operative period anaemia management continues to be of importance. Anaemia may lead to cardiovascular and cardiopulmonary complications. Rehabilitation, both in hospital and as an outpatient may adversely affect the speed of recovery if anaemia is present (88). Also, avoiding anaemia will decrease the necessity for red cell transfusions. RBC transfusions are shown to increase length of stay in the hospital and intensive care units, increase risk for infections and increase the rate of mortality (89). Correction even if only partial, of the preoperative hemoglobin level (at least to >100 gm/L) will decrease the chance of significant post-operative blood loss (90). Preoperative halting of anti-platelet agents, non-steroidal anti-inflammatory drugs and anticoagulants also help in decreasing the amount of post-operative blood loss (91). Many of the procedure used preoperatively and intraoperatively may also be used in the postoperative period to prevent or mitigate anaemia.

Sampling

Blood draws for laboratory and point of care testing may lead to iatrogenic anaemia. These tests performed to monitor and manage patients' care may lead up to 40 mL/day or more of blood loss (92). To curtail this issue protocols may be instituted. The number of draws per day should be limited especially for routine monitoring. If the patient is stable evaluation of the necessity for the tests should be performed. This evaluation may be done every 3–5 days to stop unnecessary more frequent testing. Combining lab tests into one blood tube should also be done as well as sharing of the tubes, if possible, with various sections of the laboratory. Drawing laboratory samples from central lines will also decrease blood wastage. Using smaller sample testing tubes will also save blood by decreasing the volumes of blood sampled for testing by almost 2-fold (93,94).

Nutrition

Post-operative nutrition is important for wound healing and

Table 1 Hemostatic agents (81)

Type of hemostatic agent	Mechanism of action	Indication
Cellulose	Oxidized cellulose is saturated with blood at bleeding site and swells into a gelatinous mass that aids in clot formation	Easy to handle and does not adhere to surgical instruments
Collagen	activate the intrinsic pathway of the coagulation cascade and promote platelet aggregation	Widely used at local bleeding site
Gelatin	induce hemostasis and activate coagulation cascade through physical properties	To be used in wounds with irregular contour since it will acquire the geometry of the wound and create mechanical tamponade effect
Polysaccharide	Its powerful osmotic action dehydrates and gels the blood on contact to accelerate the natural clotting process	Mechanical barrier in local bleeding, not to be used in ophthalmoscopic or neurological or urological surgeries since it expands up to 500 times
Thrombin	It Interacts with fibrinogen present in blood at the bleeding site and helps in fibrin clot formation	localized refractory bleeding and during neurological, orthopedic, cardiac, and vascular surgeries
Thrombin + gelatin	Stops bleeding by making composite particles of fibrin clot at the bleeding site by biophysical hemostasis	localized refractory bleeding
Thrombin + collagen	It causes interaction between human fibrinogen and human thrombin and the physiology of the fibrin clot formation	localized refractory bleeding and vascular surgery
Fibrin adhesive	Provide fibrinogen, thrombin and factor XIII at the site of the bleeding that mimics the body's common pathway of coagulation	Clotting disorder, patients receiving heparin or anticoagulant
Albumin + Glutaraldehyde	Glutaraldehyde molecules covalently bond/crosslink the albumin molecules to each other and, on application, to tissue proteins at the repair site, creates a mechanical seal independent of coagulation cascade	Easy to use and most affordable sealant which can be used in mechanical sealing in vascular surgeries
Ethylene-glycol polymers	It absorbs large amounts of fluid and expand. And finally close the wound by putting mechanical pressure at the bleeding site	Mechanical sealing of leakage (urology or cardiac surgery) or air leakage in lung operation
Cyanoacrylate adhesive	When exposed to anions from skin moisture or wound exudate its monomers quickly polymerize in an exothermic reaction that binds to the most superficial epithelium. It also forms a water-tight barrier stop approximated wound edges creating a cyanoacrylate bridge to allow uninterrupted wound healing	Can be used in coagulopathy as its mechanism of action does not depend on state of coagulation, and has bactericidal property

erythrocyte production. IV iron if not given preoperatively can be given post-operatively. The IV iron repletes iron stores quickly. Over the following 2 weeks hemoglobin levels may rise 20 g/L in the anaemic patients (90,95). Vitamin B12 and folate also aid erythropoiesis and maintain red cell mass. Protein deficiency anaemia (aka hypo-proliferative anaemia) may lead to mild to moderate anaemia. This may be seen in multiple chronic diseases such as liver or kidney failure. Post-surgery there may also be malnutrition due to inadequate protein intake. Correcting this deficit may lead to more efficient hemoglobin production and correction of anaemia (96).

Bleeding management

Risk of bleeding increases for up to 48 hours after major surgeries (97). When cardio-bypass pumps are used platelets degranulate while passing through the pumps and become non-functional. During this time if active bleeding occurs platelet transfusions may be required to control the bleeding. Coagulation function assays including prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen and thromboelastography (TEG) may be used to evaluate for the presence of coagulopathies following surgeries. Depending on the deficiency present, specific type of plasma like cryoprecipitated antihemophilic factor (cryo-AHF) cryo-poor plasma, plasma frozen within 24 hours (PF24) or platelets may be given to correct the coagulopathy. If bleeding is present and no coagulopathy is found a surgical exploration may be needed to find a potential anatomic defect (98).

As is performed intraoperatively, post-operative blood salvage is another way to treat anaemia. If the blood volume losses are large the blood may be collected in cell washers, cleaned and reinfused. Reinfusion needed to be done within four hours if blood is processed, collected and stored at room temperature (99). If large volumes especially over 5 units (i.e., 1,000 mL) are given 1:1 transfusions with RBC: plasma should also be instituted to decrease the incidence of transfusion induced coagulopathies (100). For orthopedic surgery patients, techniques can be used to decrease blood loss post-operatively, such as limiting the time that drains are active, using low pressure suctions on drains, and using compression on wound sites or elevating the limb. Each manipulation on its own has limited effect but together may significantly decrease blood loss (101).

Role of pharmacologic agents

As stated previously IV iron may be used to help correct iron deficiency anaemia. Acute blood loss and the inflammatory state following surgery impairs iron absorption and metabolism. IV iron has been shown not to increase the risk of infections, bleeding or other complications (thromboembolisms) as initially hypothesized. Recombinant human erythropoietin (rHEpo) in combination with IV iron can speed up the production of red cells and more quickly correct anaemias. rHEpo is most beneficial for patients who are difficult to crossmatch (i.e., multiple alloantibodies) or with those for whom blood transfusion is not an option (94,102).

If renal insufficiency is present and bleeding is active, treatment can be given to stop the bleeding. If the hemoglobin level is below 70 g/L, RBC transfusion can be given. When hemoglobin levels are between 70–100 g/L blood flows in a laminar fashion and aids interaction of platelets with the endothelial lining. Below this level platelets migrate more to the central area of vessels and are less like to be activated with endothelial damage present. Also, with renal failure platelet function is also impaired, if the platelet count is over 50,000/μL additional platelets transfused may not aid in stopping the bleeding. Desmopressin (DDAVP), in small doses 0.3 μL/kg, causes the release of von Willebrand factor (vWF) from endothelial cells. Dosing with DDAVP can be done only two times in 48 hours secondary to tachyphylaxis. The released vWF aids in platelet function and activation. If bleeding continues after two doses are given, cryoprecipitate may be given to supply additional vWF every 8 hours. Dialysis may also be performed to decrease uremia and improve platelet function. If renal failure is chronic and bleeding continues estrogen can be given and has been shown to increase levels of coagulation proteins (103-105).

For orthopedic surgery patients, techniques can be used to decrease blood loss post-operatively, such as limiting the time that drains are active, using low pressure suctions on drains, and using compression on wound sites or elevating the limb. Each manipulation on its own has limited effect but together may significantly decrease blood loss.

Perioperative anaemia in special group of populations

Particular patient populations, such as pediatric, geriatric, oncologic surgical patients, as well as those for whom transfusion of blood is not an option (such as Jehovah's Witnesses), present special challenges for the management of perioperative anaemia. For these special cases, there remain a number of vital factors that need to be kept in mind.

First, anaemia is prevalent in paediatric populations and is linked to higher perioperative mortality. Preoperative anaemia occurs in around 46.2% of paediatric patients with accessible haemoglobin measurements with increased prevalence in lower-middle-income countries (106,107). Neonatal postoperative in-hospital mortality is independently correlated with preoperative anaemia (where anaemia was defined as hematocrit level 40%) (108). Although erythropoiesis-stimulating drugs and/or the usage of iron have been associated with decreased transfusion needs in a few paediatric populations, there is not enough information to advocate their routine use in this population (40).

Anaemia is also more common in elderly surgical patients. Increased postoperative morbidity and death are linked to anaemia in this population. Anaemic patients routinely undergo surgery without taking this risk factor for a poor result into account during assessment and care. Allogenic blood transfusions, which are currently the backbone of treatment for anaemia in elderly surgical patients, can have detrimental effects and are increasingly avoided (109).

Anaemia affects one-third of oncology patients at the time of diagnosis and two-thirds of them at the 6-month period. Blood loss, nutritional inadequacies, persistent inflammation, involvement of the bone marrow, hepcidin-driven iron sequestration into macrophages with subsequent iron-restricted erythropoiesis and chemotherapy are some of the causes (110). Regardless of the underlying cause, anaemia continues to be a risk factor for poor prognosis in cancer patients, especially in the perioperative setting, and raises the likelihood of receiving allogeneic blood transfusions, which in turn increases the risk of tumour recurrence and poor patient outcomes. A higher risk of unfavourable outcomes has been independently linked to blood transfusions in cancer patients undergoing surgery (111). Due to reported but contentious potential side effects include tumour progression, tumour recurrence, myocardial infarction, stroke, and early mortality, use of ESAs in cancer patients is strongly contested. Notably, many of these worries stem from studies using high dosages of ESAs for lengthy periods of time in nonsurgical oncologic patients, particularly when aiming for normal or nearly-normal haemoglobin levels. In cancer patients with anaemia, short-term, on-label preoperative erythropoiesis-stimulating drugs treatment is safe according to the most recent research (112,113).

Patients for whom blood transfusion is not an option represent a third patient population that necessitates special treatment. Patients who would refuse blood transfusions out of moral or religious convictions most often members of the Jehovah's Witness faith as well as those for whom appropriately cross-matched blood is not available fall under this category (114). Epoetin alfa may be dosed daily (300 units/kg) for urgent treatments, however, weekly ESA drugs and IV iron are typically used to address anaemia. However, studies have shown increased morbidity and mortality in patients with severe anaemia who cannot be transfused, and this population may warrant more intensive treatment of anaemia before preforming procedures with the possibility of higher blood loss. In general, outcomes are favourable in these populations when supported with blood conservation techniques. It should be noted that treating anaemia is only a small component of the wider blood conservation procedure that should be employed to effectively and properly care for patients for whom blood is not an option (115,116).

Future directions of perioperative anaemia management

The future of perioperative anaemia management looks bright. An increase in the global awareness of PBM, underpinned by a strong and growing evidence base showing better patient outcomes, the obvious economic benefits and the ethical imperative to manage patients in a way that secures the best possible outcomes while limiting their risk exposure as much as possible, is contributing to PBM becoming an essential element of good patient care overall (117). In addition, the recognition that blood transfusion is one of the five most overused medical procedures and subsequent recommendations to limit blood transfusion to situations where it is truly needed, has bolstered efforts to ensure that it is used more appropriately (118-120). More recently, the WHO has released a policy brief as a call to action for the development of guidelines for global implementation of PBM (121). It is hoped that this will provide the needed impetus for governments, health ministries and private organizations to implement the necessary structures to make this a reality. Many countries around the world, from those of lower to higher income, have already initiated national PBM programs and are increasingly reporting similar benefits to those seen in the early studies (121-123).

A key element of optimisation of perioperative anaemia is the establishment of preoperative anaemia clinics. Depending on locally available knowledge and experience of PBM and anaemia management, this can be run by a clinical nurse practitioner, a general medical practitioner or a specialist (e.g., surgeon, anaesthesiologist, haematologist, etc.). Hospitals should be encouraged to make the investment as the likely future savings, coupled with the ethical imperative of improving patient outcomes, should be more than enough compensation for any costs incurred (124-126).

With increased awareness, a need for increased education has been identified, and it is foreseen that there will be an increase in both formal and informal educational programs (127,128). The ease of use, and increasing adoption of online learning modalities, availability of online resources, as well as the use of virtual platforms for hosting conferences or *ad hoc* meetings, have brought access to the best education and world class experts on these topics, to the doorstep of almost anyone in the world, that has a smart phone and access to the internet and in a very cost-effective manner (129). It is foreseen that this will expand going forward resulting in high-quality, affordable, credit-bearing educational programs that can be used to satisfy licensure requirement and provide certification in elements of PBM that are required. Further, global, but also country-level guidelines for perioperative anaemia management are still required in many countries. An opportunity exists for skills development in guideline development in many countries as well.

On the diagnostic front, a need has been identified to revisit normal reference ranges and diagnostic cut-off levels for laboratory parameters of anaemia (130,131). Data showing an increase in peri-operative morbidity in women with a hemoglobin <130 g/L, which is higher than the currently accepted "normal" cut-off of 120 g/L, needs to be further elucidated and confirmed. Noting that patients with perioperative anaemia often have iron restriction with normal or increased serum ferritin levels makes the diagnosis of iron deficiency that requires treatment in this group difficult. A lot of uncertainty remains on the precise diagnostic criteria for iron deficiency in conditions where underlying inflammation, malignancy or organ compromise, might lead to laboratory results that might mask iron deficiency. Newer laboratory tests (e.g., reticulocyte hemoglobin content, percentage hypochromic red cells, soluble transferrin receptors, serum and urine hepcidin levels, etc.) are being validated in different surgical and non-surgical settings, and are expected to assist with diagnosing these patients more accurately (130).

The development of new technologies, in terms of cell salvage, easy-to-use and interpret point-of-care testing (e.g., iron studies, coagulation, hemoglobin, etc.), biodegradable sealants and robotic and other forms of surgery assist in limiting blood loss. More accurate ways of measuring patients' physiological status and their ability to tolerate anaemia by the bedside or through wearable technology to allow for early detection of changes in a patient's physiological responses that might indicate a need for blood transfusion, will hopefully one day become a reality (130). One can also foresee that assistance by artificial intelligence systems, driven by machine learning algorithms will become more and more accurate in predicting the need for and response to blood transfusion. Finding ways to integrate the data from all these data streams into day-to-day practice such as mobile applications and other digital tools will become important for the clinician and it is likely that support systems that take responsibility for patient monitoring, even if out of hospital, can be expected to become more widespread (132).

Drugs that safely target hepcidin, RBC production and inflammatory cytokines that influence blood production, will hopefully become part of our armamentarium, to address restricted erythropoiesis, as is usually seen in perioperative anaemia, without increasing infectious and other risks.

Conclusions

- ❖ Perioperative anaemia is independently associated with poorer outcomes in surgery, which warrants a proactive approach to evaluation and management of anaemia.
- ❖ The appropriate approach to treatment of preoperative anaemia will depend on investigation of the patient's underlying pathophysiology. The most common cause of preoperative anaemia is iron deficiency.
- ❖ Appropriate use of iron supplementation combined with ESAs prior to surgery, techniques of intraoperative blood conservation like intraoperative cell salvage and ANH, along with hemostatic agents during intraoperative phase and limiting inappropriate phlebotomy, optimizing nutrition, and judicious utilization of pharmacologic agents during the post operative phase will likely lead to increased adoption of best practices for management of perioperative anaemia.

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