Review

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Patient blood management strategies in vascular surgery

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ABSTRACT

Transfusion of blood components can save lives, but like all therapeutics, it carries risks and costs. Therefore, transfusion should be used judiciously. Patient blood management provides safe and rational use of blood and blood products and is designed to improve patient outcomes by minimizing unnecessary exposure to blood products. In this review, perioperative patient blood management and techniques to minimize blood loss during vascular surgery are discussed.

Keywords: Perioperative patient blood management, transfusion, vascular surgery.

The World Health Organization (WHO) defined patient blood management (PBM) as a patient-centered, systematic, evidence-based approach to improving patient outcomes by reducing unnecessary transfusions.[1] The goal of PBM is to use transfusion as a therapeutic intervention only when it is for the benefit of the patient.[2,3] Patient blood management has three main goals: optimization of preoperative red blood cell (RBC) volume, including RBC mass and iron stores, minimizing surgical blood loss and coagulopathic bleeding, and the application of a restrictive transfusion threshold and optimization of patient-specific physiological reserves against anemia (Figure 1).[3]

Since surgical patients receive up to half of all transfused blood, understanding the intraoperative blood transfusion usage pattern is critical. Transfusion can save lives but has certain risks and costs.[2] Perioperative anemia, intraoperative blood loss, and perioperative blood transfusions are common practices in vascular surgery. Due to the nature of the atherosclerotic disease, this patient cohort often has one or more comorbidities, such as ischemic heart disease, renal failure, and chronic anemia.[4,5] Vascular surgery patients commonly develop anemia as a result of existing comorbidities, concomitant anticoagulant or anti-platelet therapies that increase the risk of bleeding, and interventions resulting in frequent blood loss.

Blood transfusion may be needed to replace blood loss during vascular surgery; however, it also brings risks, such as alloimmunization, increased risk of infection, lung injury, and transfusion-induced volume overload. Many studies have shown that blood transfusion is associated with increased morbidity and mortality in surgical patients.[5,6] Surgery presents distinct challenges in terms of potential bleeding and blood loss as it is an invasive process. Achieving the PBM goals of reducing or eliminating transfusion requires specific approaches in the identification and management of preoperative anemia and reduction of perioperative blood loss.

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Figure 1. Patient blood management.

Preoperative blood management strategies

Preoperative detection of anemia is the first step in achieving the PBM goals. Peripheral arterial disease affects more than 200 million people worldwide,[7,8] and perioperative anemia prevalence among these patients ranges from 47 to 75%.[7] Therefore, it is essential to detect and treat anemia in the preoperative period. Paranesthesia control also provides an opportunity to assess bleeding risks and minimize the need for blood transfusions. Patients may be at increased risk of bleeding for several reasons: advanced age, decreased preoperative RBC volume (small body size or preoperative anemia), medications affecting hemostasis, medical conditions causing hemostatic defects, including hereditary bleeding disorders, acquired medical conditions, such as chronic kidney or liver disease, and the type of surgery (e.g., complex cardiovascular surgery may be accompanied by major blood loss, which can lead to loss and consumption of coagulation factors and hemodilution) (Figure 2).

Management of preoperative anemia

Preoperative anemia is associated with an increased risk of blood transfusion.[9,10] According to the WHO, anemia is defined as a circulating hemoglobin concentration of less than 13 g/dL for men and less than 12 g/dL for women.[1] Iron deficiency is categorized as either absolute (iron deficiency anemia) or functional (anemia of inflammation, also referred to as anemia of chronic disease). Surgery may be delayed depending on the cause and degree of anemia, the urgency of the procedure, the expected amount of blood loss, and other risk factors.[11-13]

Preoperative iron replacement

Patients with iron deficiency anemia, unless there is a compelling need for immediate surgery, can be treated with oral/intravenous iron supplementation depending on the scheduled time for surgery (Figure 3).

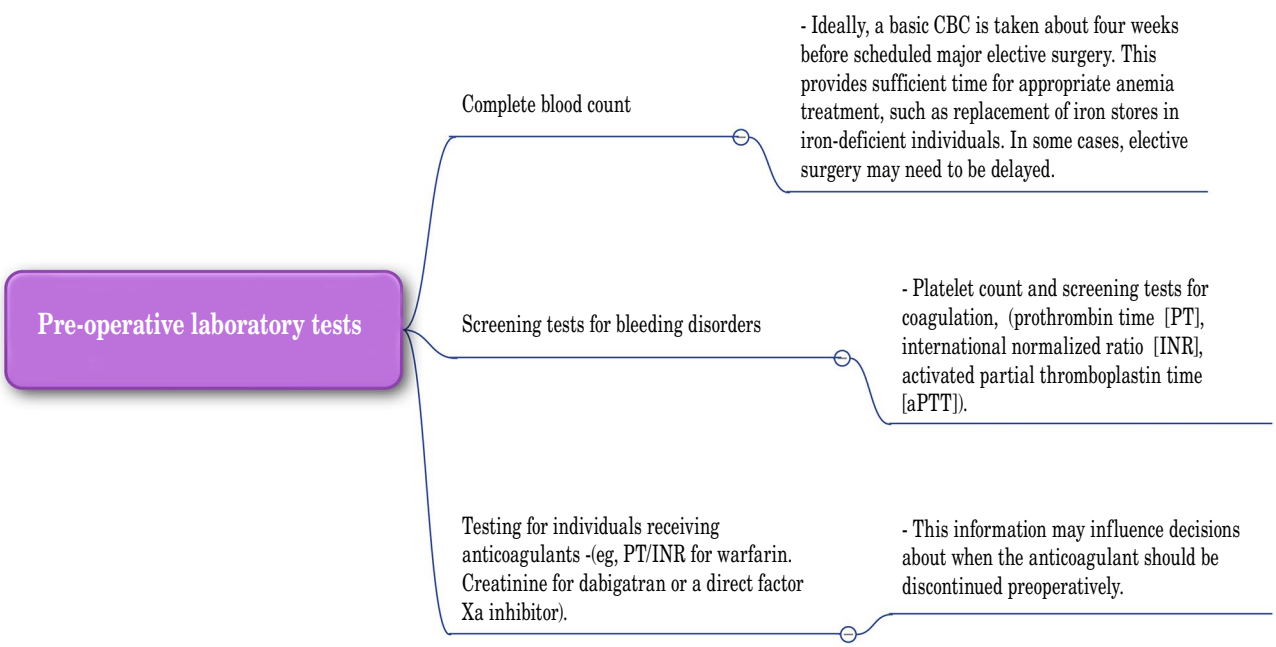

Figure 2. Preoperative laboratory assessment tests.

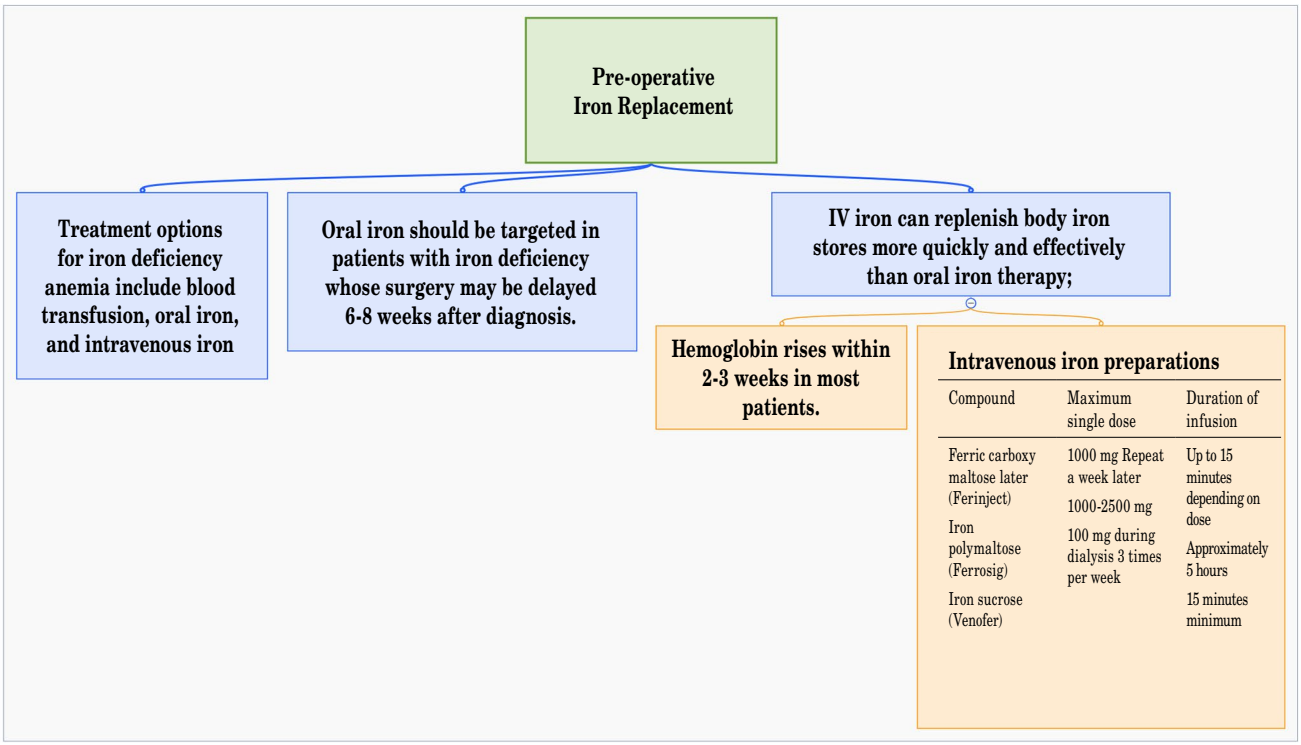

Figure 3. Preoperative iron replacement.

Erythropoietin therapy

Erythropoietic therapy may be considered for these situations:[13,14] patients with expected blood loss >500 mL or hemoglobin <12 g/dL, with anemia caused by chronic disease/inflammation, and scheduled for a major noncardiac surgical procedure; patients undergoing cardiac surgery with anemia of chronic disease or inflammation and hemoglobin <13 g/dL.

The guidelines of the European Society of Cardiothoracic Surgery, the European Association of Cardiothoracic Anesthesiology, and the Society of Cardiovascular Anesthesiologists recommend that preoperative erythropoietin (EPO) and intravenous iron supplementation should be considered in iron deficiency anemia for anemic cardiac surgery patients.[10-12]

However, there are some safety concerns regarding the use of perioperative EPO; potentially harmful effects of EPO are venous thromboembolism, hypertension, and possible adverse outcomes in patients with cancer. These side effects are likely to occur as a result of higher hemoglobin concentrations and its stimulating effect on cell growth, including tumor cells. It is reasonable to avoid EPO in people with severe uncontrolled hypertension or cancer receiving therapeutic chemotherapy.[14]

Preoperative autologous blood donation

Autologous transfusion is the collection, storage, and transfusion of the patient's blood when necessary. Autologous blood is considered the safest type of transfusion. However, when the indications are evaluated, the usage rate is around 5 to 10%.[3,15] In autologous blood transfusion, there is no risk of infection transmission, immune, hemolytic, febrile, and allergic reactions, and graft versus host disease by erythrocyte, leukocyte, and thrombocyte alloimmunization. There are four types of autologous transfusion methods in use today: preoperative autologous blood donation, acute normovolemic hemodilution, intraoperative salvage, and postoperative salvage (Figure 4).[16]

Preoperative erythrocyte transfusion indicationss

The hemoglobin value is vital when deciding on blood transfusion, but it should not be the only criterion; age, associated comorbidities, duration of anemia, the possibility of perioperative blood loss, and the type and duration of the operation should also be considered. If hemoglobin level can be increased with hematinic drugs, such as iron, folic acid, and vitamin B12, and the patient does not have symptoms, transfusion is not required.[17-19] Transfusion of packed RBCs should be reserved for patients who are actively bleeding or have severe and symptomatic anemia

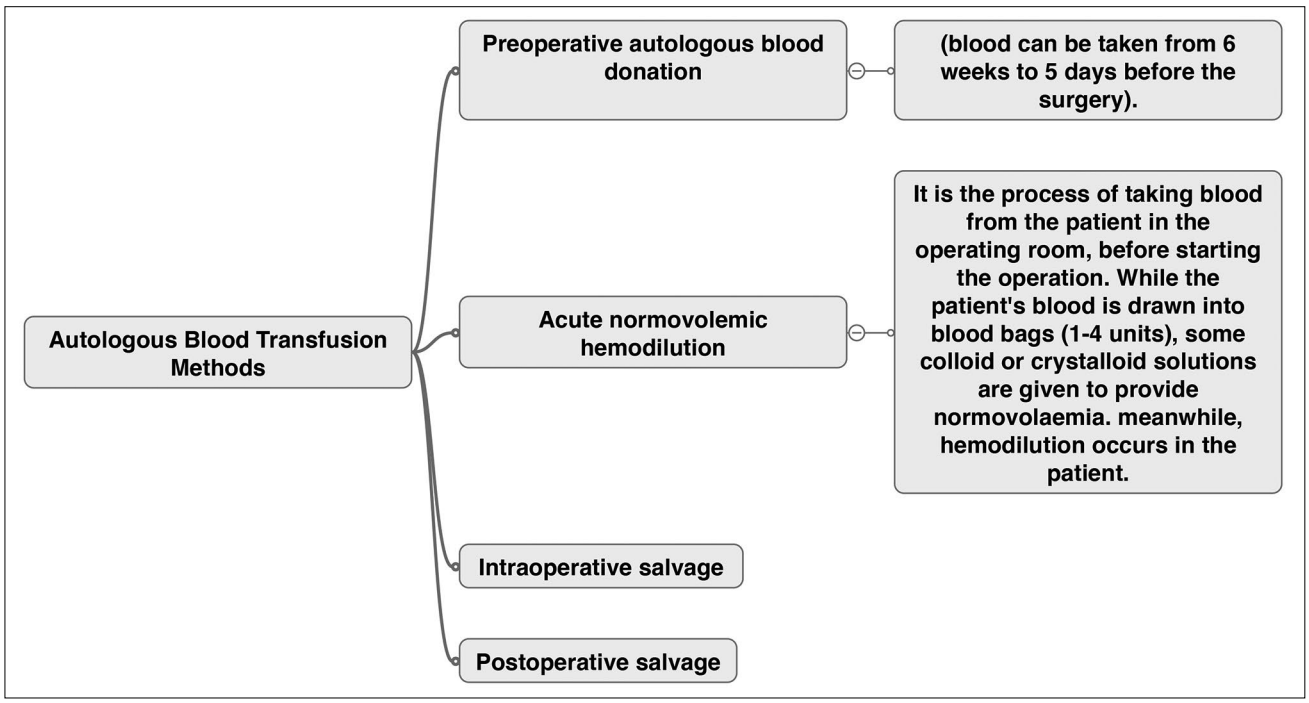

Figure 4. Autologous blood transfusion methods.

(Table 1). In general, most patients with a hemoglobin value ≤7 g/dL require transfusion.

Reversal of perioperative bleeding tendency

Drugs used for thromboembolic prophylaxis increase bleeding risk.[17] There are two main classes of oral antithrombotic drugs: antiplatelet drugs that prevent platelet activation and initial clot formation, and anticoagulant drugs that control the coagulation cascade and prevent clot stabilization.

Perioperative management of vitamin K antagonist (VKAs)

Vitamin K antagonists are mainly indicated in patients with mechanical heart valves, atrial fibrillation accompanying rheumatic mitral valvular stenosis. For those patients, direct oral anticoagulant therapy is associated with a worse outcome compared to VKA therapy.[19-22] Current guidelines recommend that VKAs should be stopped three to five days before surgery to obtain an international normalized ratio ≤1.5.[19,23] Perioperative management of VKA depends on the urgency of surgery and the estimated amount of perioperative bleeding. Options include dose omission, administration of vitamin K, and coagulation factor concentrates (Figure 5).

In patients that are at high risk of thromboembolic events (mechanical mitral valve prosthesis, atrial fibrillation with a CHA_2DS_2-VASc (Congestive heart failure or left ventricular dysfunction Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled)-Vascular disease, Age 65-74, Sex category) score >6, atrial fibrillation with rheumatic moderate to severe mitral stenosis, ischemic stroke, and venous thromboembolism in the last three months), bridging with low molecular weight heparin or unfractionated heparin is recommended.[23,24]

Approach to the patient using a new generation non-vitamin K-dependent direct oral anticoagulant

Direct oral anticoagulants are potent, fast-acting drugs, and they reach their peak effect within 1 to 3 h. Their rapid anticoagulant effect is similar to that of low molecular weight heparin. Thus, they usually do not require bridging (Table 2).[23,25]

Antiplatelet medication

Postoperative bleeding risks and perioperative ischemia risks of patients should be evaluated together. Complex and redo operations, severe renal failure, hematological diseases, and hereditary platelet dysfunctions increase the risk of bleeding, whereas acute coronary syndrome, recent stent implantation (within one month), recent thromboembolic event,

Table 1. Indications and uses of blood, and product

	Primary usage	Contents/volume	Storage and expiration
WBC	Active bleeding, shock	RBC and plasma. WBC and platelets are not viable after 24 h. Factors V and VIII significantly decreased after 2 days. Hct 35%. 520 mL	35 days 4°C Blood product
RBC	Coagulopathy where the specific factor is not available. Replacement of particular plasma proteins.	Hct 60% 340 mL	42 days 4°C
Platelet concentrate	Platelet counts <10,000/μL for the prevention of spontaneous bleeding, platelet counts below 50,000/μL with active bleeding or requiring invasive procedures.	Platelets (5.5×10^{10}); 50 mL	5 days 20°C
Platelet pheresis	Platelet counts <10,000/μL for the prevention of spontaneous bleeding, platelet counts below 50,000/μL with active bleeding or requiring invasive procedures.	Platelets ($3\ 5\times10^{11}$): 300 mL	5 days 20°C
Fresh frozen plasma	Any abnormality of coagulation tests (prothrombin time, international normalized ratio, or partial thromboplastin time) prior to invasive procedures carrying a high risk of bleeding complications or with current life-threatening bleeding.	Plasma proteins, all coagulation factors, complement. 225 mL	1 year-18°C
Cryoprecipitate	Go to a specific page cryoprecipitate is indicated for patients with severe hypofibrinogenemia (<100 mg/dL) immediately prior to any invasive procedure.	Fresh frozen plasma, thawed to 1-6°C, is then centrifuged and the precipitate is collected. The precipitate is resuspended in a small amount of residual plasma (usually 10-15 mL) and then re-frozen for storage.	Cryo can be stored at -18°C or colder for 12 months from the original collection date.
Prothrombin complex concentrates	* PCC3: Hemophilia B * PCC4: Reversal of vitamin K antagonist	PCC.4C; Factor (2, 7, 9, 10), Prt. C, Prt. S	PCC.3C; Factor (2, 9, 10)

WBC: White blood cell; RBC: Red blood cell; Hct: Hematocrit; Prt. C: Protein C; Prt. S: Protein S; PCC: Prothrombin complex concentrate;

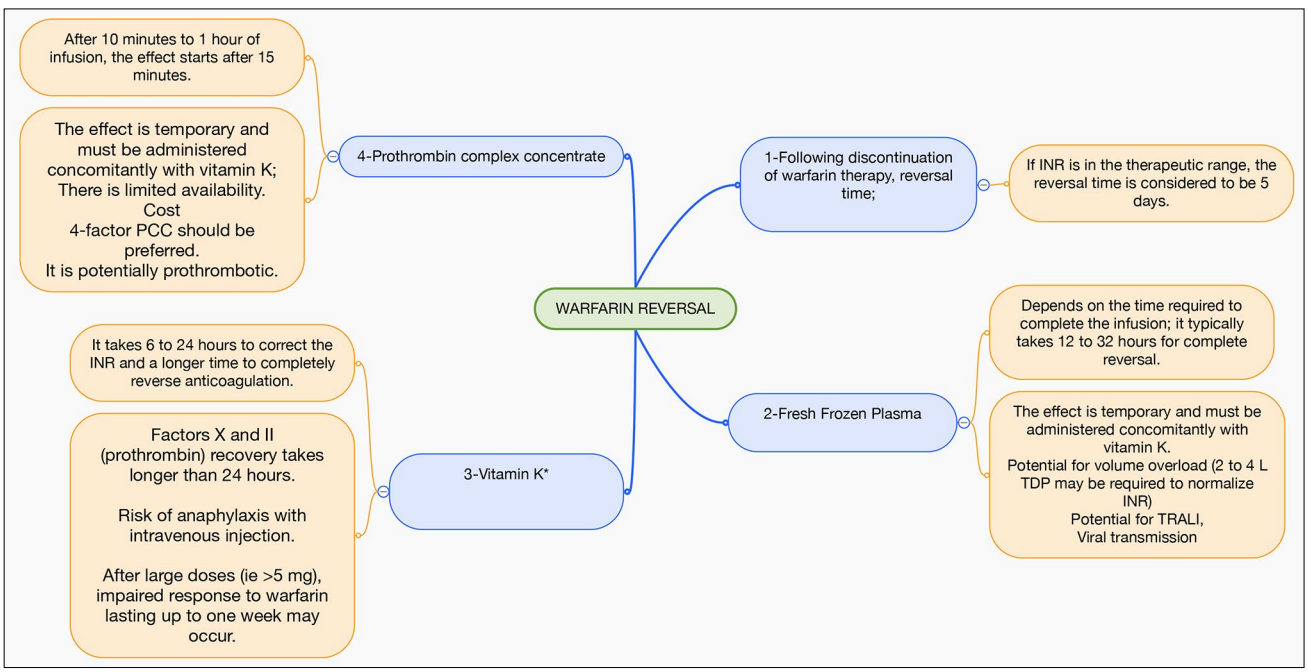

Figure 5. Warfarin reversal therapy.

PCC: Prothrombin complex concentrate; INR: International normalized ratio; TDP: Fresh frozen plasma; TRALI: Transfusion related acute lung injury.

Table 2. Pre-surgical drug withdrawal times of new generation direct oral anticoagulants (DOAC)

1.	Apixaban-edoxaban-rivaroxaban ≥48 h
2.	Dabigatran ≥48 h

and poor angiographic score increase the risk of ischemia. Antiplatelet agents have not yet been developed for effective bridge therapy. Cangrelor, a reversible antiplatelet agent, is suitable for bridge therapy (Figure 6).[25]

Intraoperative strategies

In all patients who will undergo surgery, the goal should be to preserve the erythrocyte mass and coagulation status of the patient. Meticulous surgical hemostasis, advanced anesthesia and surgical techniques, minimally invasive surgical techniques, meticulous dissection, intraoperative attention to limit blood loss, and application of topical hemostatic agents are important in intraoperative blood management.

For intraoperative transfusion management, reduction of allogeneic erythrocyte transfusion using blood salvage techniques should be considered.[23,24,26]

Transfusion triggers

The 2016 Association for the Advancement of Blood & Biotherapies (AABB) guidelines indicate that a hemoglobin level of 7-8 g/dL is a restrictive RBC transfusion threshold and a hemoglobin level of 9-10 g/dL is a liberal RBC transfusion threshold.[27,28] Furthermore, results from a meta-analysis of 12,000 patients found no evidence that a restrictive transfusion strategy carries a higher risk than a liberal transfusion strategy, except for patients with acute myocardial infarction.[27] The AABB recommends using a restrictive hemoglobin transfusion threshold of 7 g/dL for hospitalized adult patients who are hemodynamically stable, including critically ill patients, but a hemoglobin transfusion threshold of 8 g/dL for patients undergoing orthopedic or cardiac surgery and for those with underlying cardiovascular disease (Table 3).[2,24,27,28]

A restrictive transfusion threshold approach is associated with reduced blood use, lower costs, and reduction in uncommon but potentially serious adverse events.[28] However, a 2016 meta-analysis reported that a restrictive transfusion strategy (hemoglobin level <8.0 g/dL) increases the risk of acute coronary syndrome in patients with acute and chronic cardiovascular disease.[28] In addition, it has been suggested that it is desirable to maintain a liberal transfusion strategy (hemoglobin level ≥8.0 g/dL) until large-scale randomized controlled trials prove otherwise.[27,28]

A Cochrane review of more than 6,000 patients concluded that a restrictive transfusion strategy reduced the risk of receiving RBC transfusion by 39%, amount of blood transfusion by 1.19 units on average, and in-hospital mortality (relative risk: 0.77) but not 30-day mortality (relative risk: 0.85).[29] The authors recommend waiting for blood transfusion in patients without acute coronary artery disease until hemoglobin levels drop to 7-8 g/dL unless there is significant bleeding.[29]

In cardiac surgery, the TITRe2 (transfusion indication threshold reduction) trial demonstrated uncertainty of restrictive strategies in unstable cardiac patients and reported a beneficial impact of liberal

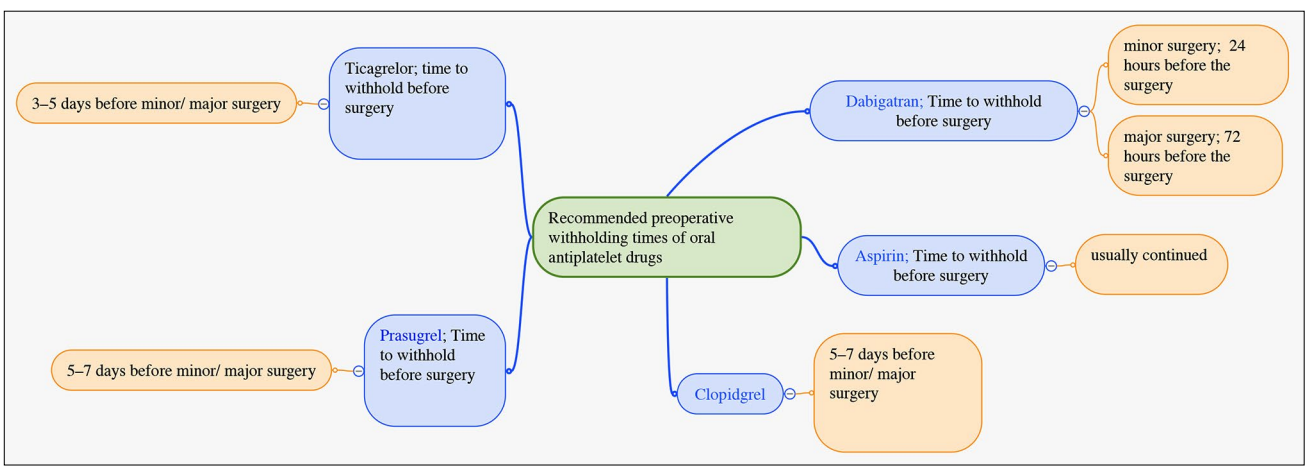

Figure 6. Recommended preoperative withholding times of oral antiplatelet drugs.

Table 3. Common transfusion thresholds for selected blood components

Component	Situations	Transfusion thresholds
Red blood cells	Hospitalized adults	Hemoglobin <7.0 g/dL
	Orthopedic surgery, cardiac surgery, preexisting cardiovascular disease	Hemoglobin <8.0 g/dL
Platelets	Hospitalized adults 10,000/μL	10,000/μL
	Central venous catheter 20,000/μL	20,000/μL

transfusion to a hemoglobin concentration >9 g/dL on mortality following cardiac surgery (4.2% in the restrictive group vs. 2.6% in the liberal group; hazard ratio: 1.64, 95%; p=0=045).[30] Based on these results, it seems that the blood transfusion threshold may be different in various clinical groups and its effect is not only related to the change in hemoglobin concentration.

Perioperative bleeding control

Intraoperative patient monitoring for blood loss, signs of inadequate perfusion and oxygenation of vital organs, hemoglobin or hematocrit variations, coagulopathy, and adverse effects of transfusion all have vital importance in PBM. It is imperative to take necessary precautions to achieve early hemostatic resuscitation and prevent the fatal triad (dilutional coagulopathy, hypothermia, and acidosis) in patients with acute bleeding or severe perioperative bleeding.[23,24] Fluid replacement and blood transfusions may be used in case of significant bleeding (>500 mL blood loss or if the hemoglobin level does not fully reflect the patient's clinical status) or if bleeding cannot be stopped immediately.[8,9]

Fluid management

In replacing the lost blood volume, transfusions should only be used if hemoglobin is low enough and the patient shows clinical signs of acute anemia.[3] The lost blood can be replaced with either a 1.5:1 electrolyte crystalloid solution or an equal volume of 1:1 colloid solution to maintain normovolemia until the hemoglobin falls below the transfusion threshold.[3,9] Generally, if blood transfusion is planned, it can be calculated as one unit of blood transfusion for every 500 mL of blood lost.[16]

Where severe blood loss is involved, the initial fluid resuscitation is a combination of crystalloids and colloids. The initial resuscitation volume should be limited to 1 L, followed by infusion of blood products. During massive transfusion, a high fresh frozen plasma: platelet: RBC ratio of 1:1:1 is recommended since it has been proven to provide a survival benefit.[26,31]

In cases of perioperative hemorrhage (aortic arch replacement, thoracoabdominal aneurysm repair, ruptured aortic aneurysm, or acute aortic dissection), patients are usually in a state of severe hemodynamic instability. In these cases, the degree of acidosis reflects the grade of hypoperfusion.[23,25,26] Acidosis is also a prominent cause of coagulopathy besides hypothermia and hemodilution.

Acute aortic dissection itself activates the coagulation system and consumes large amounts of coagulation factors and fibrinogen, even before surgery. Acute aortic dissection and hypothermic circulatory arrest lead to severe coagulopathy by impairing and consuming clotting factors and fibrinogen more than impairing platelet function. Thus, in this consumption coagulopathy setting, hemostatic therapy should focus on the rapid and sufficient supplementation of clotting factors and fibrinogen after hypothermic circulatory arrest.[26] Coagulopathy may develop in cases of ruptured abdominal aortic aneurysm, and blood transfusion has a dilutional effect on the levels of clotting factors and platelets.[24] Hypothermia is also associated with adverse platelet effects, and the risk of coagulopathy increases with prolonged aortic clamping.[24]

Other following parameters that should also be measured and monitored

Body temperature, acid-base status, and ionized calcium levels must be thoroughly regulated. Calcium is coagulation factor IV and a cofactor for almost every enzymatic step in primary hemostasis, and ionized $Ca2^{+}$ should be kept at ≥0.9 mmol/L. As it is an enzymatic process, plasmatic hemostasis is strongly influenced by temperature and pH. Maintaining a core temperature ≥36°C and a pH ≥7.2 is essential.

Perioperative hypothermia is defined as a decrease in the core body temperature below 36°C, which can cause various complications. Hypothermia occurs mainly due to a combination of anesthesia-induced

impairment of thermoregulatory control, a cool operating room, and surgical factors that promote excessive heat loss. Hypothermia is associated with many adverse effects, such as increased cardiovascular complications, increased blood loss and transfusion requirements, perioperative hemorrhage, and increased infection rate.[16] In hypothermic conditions at 35°C and below, platelet function is affected, and the activity of enzymatic coagulation factors is impaired.[31-33] If operative time is longer than 30 min, the application of active thermal management should be considered. Active thermal management includes actively prewarming patients before induction of anesthesia, warming patients during anesthesia, and using an infusion warmer when large amounts of fluids and blood products are expected to be administered. A decrease in the temperature by 1°C increases blood loss by approximately 16% and increases the relative risk of transfusion by approximately 22%.[32,33]

Surgical blood conservation techniques

Electrocautery and, where appropriate, hemostatic topical agents (tissue adhesives, fibrin sealants, and autologous platelet gels) may be used. In selected cases, blood preservation techniques, such as intraoperative blood salvage or acute normovolemic hemodilution, may be appropriate.

Intraoperative blood salvage involves the collection of blood from the surgical field using a suction device. The blood is centrifuged and washed so that only concentrated RBCs are collected and returned to the patient. Marković et al.[26] found that intraoperative cell salvage reduced the need for allogenic blood transfusion in abdominal aortic surgery, and they recommend using cell salvage if at least 400 mL of blood can be collected from the surgical field. Currently, the European Society of Anesthesiology recommends the use of cell salvage in cardiac surgery involving cardiopulmonary bypass and major orthopedic surgery (1A), but not specifically for vascular surgery.[21] Blood is usually intraoperatively returned to the patient, and this may continue postoperatively. The benefits of intraoperative blood salvage are greatest in procedures with high blood loss (≥ 1000 mL).[3,4,17]

Acute normovolemic hemodilution

In acute normovolemic hemodilution, blood collection immediately before or after induction of anesthesia and replacement of blood loss with crystalloid (1:3) or colloid (1:1) fluids to maintain normovolemia.[34,35] Acute normovolemic hemodilution can be applied in the following circumstances: surgical cases with a hematocrit level >36% expected to have a blood loss ≥1 L, open heart surgery, major aortic reconstructions, thoracoabdominal aortic aneurysm surgery, aortofemoral and femoropopliteal bypasses, and venous thrombectomy.

Acute normovolemic hemodilution can be used as a method to reduce perioperative transfusions in selected cases. It should not be performed in the presence of severe anemia (Hb <11 g/dL or hematocrit <33%). It should not be performed in coronary artery disease with critical lesions, uncontrolled hypertension, cardiac surgery cases with an ejection fraction <45%, and pulmonary capillary wedge pressure (PCWP) >20 mmHg. Acute normovolemic hemodilution may impair hemostasis and should not be performed in patients with decreased coagulation factors, thrombocytopenia, platelet dysfunction, and hyperfibrinolysis due to hepatic dysfunction (e.g., liver cirrhosis).

Use of hemostatic agents

Antifibrinolytic agents

These agents are routinely used in cardiac surgery with cardiopulmonary bypass, orthopedic surgery, and other major surgical procedures. Antifibrinolytic agents prevent fibrinolysis via plasmin and promote hemostasis. Fibrinolytic agents include tranexamic acid, aprotinin, and epsilon-aminocaproic acid (EACA).[35,36] Aprotinin was associated with the risk of renal, cardiovascular, and cerebrovascular events and was withdrawn from the market in 2008.

In the CRASH-2 (The 2010 Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage 2) trial, the use of tranexamic acid reduced the possibility of receiving a blood transfusion by 30%.[36] Tranexamic acid reduces mortality from bleeding and transfusion requirements with little evidence of adverse effects, such as epileptic seizure, hypotension. It should be administered in a dose of 15-20 mg/kg in the management of major perioperative bleeding.[31]

Epsilon-aminocaproic acid may be a potential alternative to tranexamic acid. Intraoperative EACA administration is effective at reducing perioperative blood loss;[36] however, rapid intravenous administration of EACA should be avoided as it may induce bradycardia or other arrhythmias as well as hypotension.

Fibrinogen concentrate

Virally inactivated fibrinogen concentrates were developed from pooled human plasma for use in

fibrinogen deficiency or dysfunction. During ongoing bleeding, fibrinogen is the first coagulation factor to reach critical thresholds. An adequate amount of fibrinogen is crucial for stable clot formation and cessation of bleeding. The European Society of Anesthesiology guideline recommends the use of fibrinogen concentrate to maintain a target fibrinogen concentration of 150 to 200 mg/dL in patients with significant bleeding.[27,37,38]

Other hemostatic agents

Prothrombin complex concentrates are generally reserved for the immediate reversal of the warfarin effect.[39] Desmopressin may be used for uremic platelet dysfunction.[3]

In conclusion, blood components are life-saving treatments, but they are also scarce resources and should be used wisely. Patient blood management is a patient-centered, evidence-based approach to transfusion practice, with the overall goal of improving patient outcomes. Successful implementation of an effective PBM program has been shown to improve outcomes, reduce transfusion rates, and decrease associated costs.

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